The New England
Journal of Medicine

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Volume 240 MARCH 17, 1949 Number 11

PROTHROMBIN: A CRITIQUE OF METHODS FOR ITS DETERMINATION AND THEIR CLINICAL SIGNIFICANCE*

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AS A result of the widespread use of dicumarol in the prevention and treatment of thromboembolism, clinicians have become increasingly interested in the role of prothrombin in blood coagulation. Investigators are aware that present technics for prothrombin estimation have their limitations. Failure to recognize them may prevent accurate diagnosis, obstruct effective therapy or even invite disaster. It is the purpose of this paper to delineate these limitations and to scrutinize current analytical procedures in the light of recent advances in knowledge of blood coagulation.

General Considerations

By chemical isolation and purification Seegers et al.[1] have defined the plasma protein component that is convertible to thrombin — namely, prothrombin. Until some other distinguishing physiological or biochemical property is found, determination of prothrombin must involve its conversion to thrombin, which is assayed by its ability to clot fibrinogen.

Recently, plasma factors have been reported that affect the conversion of prothrombin to thrombin by thromboplastin plus calcium.[2-6] Just how they act is not clear, but it is probable that they accelerate, activate or otherwise act as ancillary agents in thrombin evolution. In any event their relation to the conversion of prothrombin to thrombin must be considered in the determination of prothrombin.

At present, no method of measuring prothrombin can assure adequate control of the nonprothrombin variables. Under such circumstances prothrombin values obtained by the generally accepted procedures are the result of several interrelated factors, of which only one is prothrombin. Accordingly, such values express only "prothrombic activity"¶ instead of "amounts of prothrombin."

Most of the current analytical technics are based upon two methods: the one-stage procedure of Quick[7] and the two-stage method of Warner et al.[8]|| In Quick's method the clotting time of the plasma is measured after optimal amounts of thromboplastin and calcium are provided. This, the prothrombin time, is the minimal interval that elapses before a macroscopic clot results from the conversion of prothrombin to thrombin. It reflects the amount of thrombin evolved together with the velocity of its evolution. The validity of the method rests upon the assumption that the velocity of prothrombin conversion to thrombin, as well as the latter's coagulation of fibrinogen, is a measure *solely* of prothrombin concentration.

In the two-stage procedure, prothrombin is presumably converted completely to thrombin in defibrinated and diluted plasma. By trial and error a suitable dilution is made that will yield a given amount of thrombin, as measured by its ability to clot a standard fibrinogen solution. Theoretically, sufficient time is allowed to complete prothrombin conversion, obviating possible variations in the velocity of this reaction. Prothrombin is thus measured by the amount, not by the velocity, of thrombin formation.

Frequently, the results obtained by both methods agree closely. Sometimes, however, there is considerable (as much as 100 per cent) discordance between the results — for example, in different species, in infants and in aged plasma, dicumarolized blood and hemophilic serum. Until these discrepancies are satisfactorily explained, results obtained by either method must be interpreted cautiously.

One-Stage Method

General Procedure

Oxalated plasma is added to potent thromboplastin extract, the mixture is brought to 37°C.,

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Supported by a grant from the Commonwealth Fund.
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¶We consider this term necessary to distinguish between the amount of prothrombin as such and the activity of a given biologic mixture in the production of thrombin for converting fibrinogen to fibrin.

||We have not included the method of Shonheyder,[9] which is based upon the inverse relation between prothrombin concentration and the amount of thromboplastin required to clot plasma in one hundred and eighty seconds.

and calcium chloride solution added. From this instant the time required for clotting (the prothrombin time) is measured.

Serum prothrombin is similarly determined except that fibrinogen must also be provided.

Certain Clotting Components

Fibrinogen. The clinical and experimental value of the one-stage method needs no elaboration. Nevertheless, it suffers from several limitations. For example, afibrinogenemic blood containing normal amounts of prothrombin will show an infinitely prolonged prothrombin time, which would be interpreted as indicating zero prothrombin. The addition of fibrinogen rectifies this defect. The relation between fibrinogen concentration and prothrombic activity is shown in Table 1. Since hypofibrinogenemic plasma may exhibit decreased prothrombic activity despite normal prothrombin content, an elevated prothrombin time must be interpreted cautiously in those conditions in which fibrinopenia as well as hypoprothrombinemia may occur (such as liver disease).

TABLE 1. *Relation between Plasma Fibrinogen Concentration and Prothrombic Activity.*

Plasma Mixture		Fibrinogen Concentration	Prothrombic Activity	
*Experiment 1**:				
Parts of afibrinogenemic	Parts of normal		Time	Concentration
		mg. per 100 cc.	*sec.*	%
0	1	250	13.0	100
1.0	3	188	12.5	100
1.0	1	125	12.8	100
2.3	1	76	14.7	40
4.0	1	50	16.5	25
9.0	1	25	22.2	11
Experiment 2†:				
0	1	171.0	13.7	100
3.0	7	120.0	13.2	100
5.0	5	86.0	13.3	100
6.0	4	68.0	14.2	46
7.0	3	51.0	14.4	43
8.0	2	34.0	16.5	25
9.0	1	17.0	22.8	10
19.0	1	8.5	45.0	4

*Normal plasma mixed with plasma from subject with congenital afibrinogenemia.

†Normal plasma mixed with normal plasma rendered fibrinogen free by addition of thrombin (5 units to 1 cc. of plasma).

The quality of fibrinogen and the milieu in which it is dissolved are also important. We have observed that as plasma ages, it clots less readily on the addition of thrombin. Whether this is referable to alteration in the fibrinogen or to changes in other plasma components[10] is still unknown. In either case such changes, spontaneously occurring or artificially induced, can conceivably affect the prothrombin time. The decreased prothrombic activity of plasma stored for as much as four weeks is not necessarily due to changes in fibrinogen, however, since deprothrombinated, fibrinogen-free plasma can restore prothrombic activity to such plasma.[11-13]

The reactivity of fibrinogen to thrombin differs also from one species to another.[14] This must be duly considered when apparent prothrombin concentration of one species is compared with that of another.

Labile factor. As plasma ages its prothrombin time increases, and yet its prothrombin concentration, as determined by the two-stage technic or by chemical isolation, may be normal.[15] The decrease in prothrombic activity is due to deterioration of a labile component found in fresh plasma,* which is necessary for the rapid conversion of prothrombin to thrombin.[2] This factor, more labile at refrigerator or body temperature than prothrombin, is not fibrinogen, and is not appreciably adsorbed by barium sulfate, in contradistinction to prothrombin.[11]

No case of deficiency of labile factor has been recorded. Two subjects in whom the elevated prothrombin time seemed due, at least in part, to low concentrations of labile factor were observed. The plasma of Subject 1, who had extensive hepatic damage from obstructive jaundice with a malignant tumor involving the liver, showed much less prothrombic activity by the orthodox one-stage technic than when the determination was made on a mixture of his plasma with normal plasma rendered prothrombin free by adsorption with barium sulfate (Table 2), as pointed out below. Furthermore, the patient's plasma was far less able to rectify the prolonged prothrombin time of stored plasma than normal plasma was. The plasma of Subject 2, with chronic myelogenous leukemia, behaved similarly (Table 3). Clearly, these subjects lacked a component (not prothrombin) present in fresh normal plasma that is necessary for normal prothrombic activity in the one-stage method and is deficient in stored plasma.

TABLE 2. *Hypoprothrombic Activity Related to Deficiency of Nonprothrombin Plasma Constituents in a Patient with Severe Obstructive Jaundice and Carcinoma of the Pancreas, with Extensive Metastases to the Liver.*

Plasma Mixture*					Prothrombin	
Parts of normal plasma		Parts of patient's plasma		Parts of stored normal plasma†	Time	Activity
fresh	*barium sulfate*	*fresh*	*barium sulfate*		*sec.*	%
1	0	0	0	0	12.8	100.0‡
0	1	0	0	0	>180.0	<1.0
0	0	1	0	0	22.6	10.0
0	0	1	0	0	33.8	50.0‡
0	0	0	0	1	68.0	2.3
0	1	0	0	1	13.6	100.0‡
0	0	0	1	1	21.8	12.0

*All plasmas oxalated.

†Stored for twenty-seven days at 4–5°C.

‡Corrected for dilution with prothrombin-free barium sulfate plasma.

*It is for this reason that the plasma must be fresh for the accurate determination of plasma prothrombin by the orthodox one-stage procedure.

It is probable that many similar observations will be made when more practical methods of measuring the labile factor, such as that of Stefanini and Quick,[16] are widely applied. Prothrombic activity is distinctly decreased[11] when the concentration of this factor is less than 50 per cent of normal. Furthermore, the effect of suboptimal concentration of labile factor is more pronounced if the prothrombin is also below normal. Accordingly, an elevated prothrombin time of a given plasma sample may be due to deficiencies of prothrombin, labile factor or fibrinogen singly or in combination.

Other Plasma Components That Accelerate the Conversion of Prothrombin to Thrombin

To these variables must be added the accelerator globulin of Seegers,[4] Factor V of Owren,[3] prothrombin A of Quick[2] and plasma factor of Fantl and Nance.[5] Apparently, these entities also accelerate the conversion of prothrombin to thrombin. Hemorrhagic episodes and hypoprothrombinemic activity due to deficiency of Factor V[17] and prothrombin A[2] have been established. Furthermore, after acute liver poisoning by chloroform in dogs, not only prothrombin but also plasma accelerator globulin falls, contributing to the low plasma prothrombic activity.[18] Here, too, the elevated prothrombin time, signifying a relatively retarded evolution of thrombin from prothrombin, reflected inadequacies in accelerator globulin as well as prothrombin.

Antithrombin. In both the one-stage and two-stage technics the thrombin evolved from prothrombin is assayed by its ability to convert fibrinogen to fibrin. Validity of this measurement depends upon the presupposition that no agent is present that will inactivate the evolved thrombin or otherwise interfere with its clotting of fibrinogen. This supposition is incorrect since plasma contains antithrombin, which can inactivate appreciable quantities of thrombin. The longer the thrombin is in contact with antithrombin, the greater the amount inactivated. Furthermore, heparin enhances this inactivation.[19] Unfortunately, little is known regarding the plasma concentration of antithrombin or heparin, or both, under pathologic conditions. Conceivably, variations in plasma antithrombin or in circulating heparin or heparin-like anticoagulants, as in certain hemorrhagic disorders,[20, 21] can influence prothrombic activity considerably. This would be especially true in hypoprothrombinemia in which the amount of thrombin evolved was so small or its evolution so slow that antithrombin activity could play a substantial role. To what extent plasma antithrombic activity may influence prothrombin time awaits further investigation.

Other clotting inhibitors. Other circulating anticoagulants have recently been described[22, 23] that affect the rate of thrombin evolution from prothrombin. They may similarly affect prothrombin determinations by the one-stage procedure. Considerable work is necessary to explore this possibility.

Serum prothrombic activity. Some of the foregoing considerations bear particularly on the determination of serum prothrombin. Obviously, the absence of fibrinogen must be rectified. Furthermore, little is known concerning the concentration in serum of other important clotting constituents. We have found that under certain conditions labile factor may be considerably reduced, or may indeed disappear, during coagulation.[24]

Coagulation is also attended by the *appearance* of substances that accelerate or activate the conversion of prothrombin to thrombin by thromboplastin and calcium.[3, 25, 26] A mixture of plasma with serum *devoid of prothrombin* shows greater prothrombic activity than can be attributed to the plasma prothrombin in the mixture.[24, 26] The amount of the accelerator in serum is related to the amount of prothrombin consumed in the process of coagulation, and varies under pathologic conditions.[27, 28] Obviously, elaboration of this substance during clotting may affect appreciably the apparent prothrombic activity of serums. We have observed, for example, that after the coagulation of hemophilic blood, the serum often exhibits from 50 to 100 (or more) per cent of the original plasma prothrombic activity when measured by the one-stage procedure.[28] By the two-stage technic, however, far less serum prothrombin is demonstrable. Accordingly, determination of serum prothrombin concentration from serum prothrombin time may be erroneous. Furthermore, computations of the prothrombin consumed during coagulation from differences between plasma and serum prothrombic activities must be viewed with caution.

In view of the prothrombin-enhancing effect of serum every precaution should be taken in draw-

TABLE 3. *Hypoprothrombic Activity Related to Deficiency of Nonprothrombin Plasma Constituents in a Patient with Chronic Myelogenous Leukemia.*

Plasma Mixture*					Prothrombin	
Parts of normal plasma		Parts of patient's plasma		Parts of stored normal plasma†	Time	Activity
fresh	*barium sulfate*	*fresh*	*barium sulfate*		*sec.*	%
0	0	1	0	0	16.2	27±
1	0	0	0	0	14.0	100±
0	9	1	0	0	24.1	97‡
1	9	0	0	0	27.8	78‡
0	0	0	0	1	52.5	3
1	0	0	0	1	14.7	42±
0	0	1	0	1	16.5	25±
0	9	0	0	1	24.4	96‡

*All plasmas oxalated.
†Stored for thirty-one days.
‡Corrected for dilution with prothrombin-free barium sulfate plasma.

ing blood for prothrombin determination against partial coagulation, which may occur when venipuncture is not immediately successful and when the blood does not flow freely into the syringe.

Weaknesses and Limitations Related to Thromboplastin Reagent

In determining prothrombin its conversion to thrombin by thromboplastin should not be limited by the quantity or quality of this clotting agent. Nevertheless, the source of thromboplastin and the method of its preparation profoundly affect the prothrombin time although it is presumably provided in excess. Quick[29] uses only fresh rabbit-brain extract, which for normal plasma gives a prothrombin time of 11.0 to 12.5 seconds. For practical reasons most clinical laboratories employ commercial thromboplastin preparations, which rarely give such a low prothrombin time and which vary considerably in potency from batch to batch even from the same manufacturer.* Furthermore, thromboplastin extracts deteriorate fairly rapidly in the liquid state. In view of these variations the prothrombin time of a given plasma sample has little significance unless it is accompanied by a value obtained with the same thromboplastin on a normal subject.

This "normal control value" may not be representative of the average normal subject since marked variations in prothrombic activity may occur from person to person or in the same person from day to day. A given prothrombin time can be interpreted, therefore, only in the light of the range of values obtained with the same thromboplastin on a *group* of normal subjects.

It has also been reported that a given thromboplastin extract may show low potency when tested on whole plasma but good activity when tested on diluted plasma.[30, 31] Similarly, under certain conditions diluted thromboplastin is more potent than concentrated thromboplastin.[31] Profound differences in prothrombin time are also obtained even on the same plasma when Russell-viper venom is used instead of brain extract.[31, 32] From the foregoing, it is evident how considerable confusion regarding prothrombin concentration and prothrombic activity may arise owing to the use of different thromboplastin preparations.

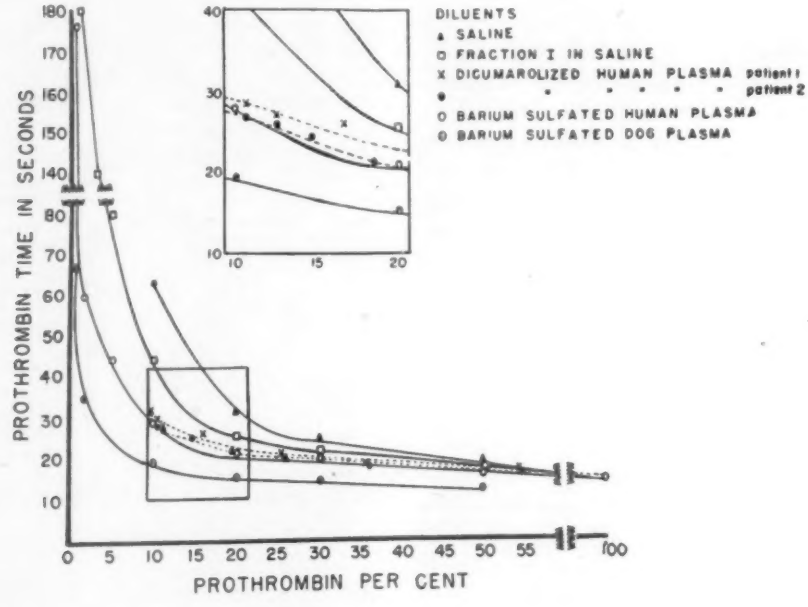
DILUENTS
▲ SALINE
□ FRACTION I IN SALINE
x DICUMAROLIZED HUMAN PLASMA patient 1
● " " " " " patient 2
○ BARIUM SULFATED HUMAN PLASMA
⊖ BARIUM SULFATED DOG PLASMA
PROTHROMBIN TIME IN SECONDS
PROTHROMBIN PER CENT
0 5 10 15 20 25 30 35 40 45 50 55 100
10 20 30 40 50 60 70 80 140 150 160 170 180
10 15 20 30 40

FIGURE 1. *Relation between Prothrombin Time and Prothrombic Activity of Normal Human Plasma Diluted with Various Diluents.*

Fraction 1 in saline solution contained 500 mg. of Harvard Fraction I per 100 cc. Patients 1 and 2 were subjects with myocardial infarction treated with dicumarol. Their plasmas, used as diluents, contained, respectively, 7.6 and 9.4 per cent (of normal) prothrombic activity. These figures were used in computing the prothrombin percentage in the dicumarolized plasma and normal plasma mixtures.

Relation between Prothrombic Activity and Prothrombin Time

Fundamental to the one-stage method is the curve relating prothrombin time with prothrombic activity (Fig. 1). From such curves the observed prothrombin time is translated into prothrombic ac-

*This may be due to the presence of anticoagulants in thromboplastin extracts from brain.[33]

tivity. In the range of 25 to 100+ per cent (of normal) prothrombic activity a substantial reduction results in a very small increment in prothrombin time. Therefore, conversion of a given prothrombin time into prothrombic activity is in this range only an approximation. This has been strongly emphasized by Link.[33] Attempts have been made[34, 35] to circumvent the difficulty by prior dilution of the test plasma to a range where a relatively small alteration in activity is reflected by a large change in prothrombin time. In this way hypoprothrombinemia can be detected long before it becomes apparent from determinations on undiluted plasma.

Dilution technic. The diluent employed for this purpose is extremely important. Ideally, it should be plasma that is devoid of prothrombin but normal in all other clotting components. Dilution with saline solution, a procedure widely used,[35] is unsatisfactory because it dilutes other clotting factors as well as prothrombin. Subnormal levels of these substances may thus become exaggerated, consequently affecting the prothrombic activity considerably. The addition of fibrinogen to the diluent[36] assures adequacy of only one component. When a saline solution of fibrinogen is used as diluent, the curve relating prothrombic activity with prothrombin time differs considerably from that derived with saline solution alone (Fig. 1). Different curves are furthermore obtained when plasma is diluted with plasma that has been rendered prothrombin free by prior adsorption with barium sulfate (Fig. 1). This agent removes prothrombin almost quantitatively as well as a small amount of nonprothrombin protein.[37] The question arises whether the additional material adsorbed consists of nonprothrombin clotting factors. As far as we know, the smallest amount of barium sulfate required to adsorb the prothrombin does not remove other important plasma clotting constituents.*

Dicumarol decreases plasma prothrombin, presumably by inhibiting its production in the liver.[33] Most investigators agree that other clotting factors are not affected to any considerable degree. Plasma from a dicumarolized subject whose prothrombin has been markedly reduced should, therefore, be an ideal diluent in the determination of prothrombic activity of any unknown plasma. The curves relating prothrombic activity with prothrombin concentration are practically identical when either dicumarolized or barium sulfate plasma is used as diluent (Fig. 1). Furthermore, adsorbing dicumarolized plasma with barium sulfate does not alter the relation (Fig. 2). This indicates that the adsorbing agent does not remove important clotting factors present in the dicumarolized plasma. From the point of view of ready availability, barium sulfate plasma is preferable to dicumarolized plasma as a diluting agent.†

By the one-stage technic dog plasma shows greater prothrombic activity than human plasma.[39] By the two-stage procedure, however, the activities are essentially the same in both species.[40] Since there is no evidence that dog prothrombin differs in its reactivity from human prothrombin, the discrepancy is most likely referable, at least in part, to nonprothrombin factors. In support of this interpretation is the fact that human plasma diluted with barium sulfate *prothrombin-free dog* plasma exhibits much greater prothrombic activity than that diluted with barium sulfate *prothrombin-free human* plasma (Fig. 1). Similar results are obtained with

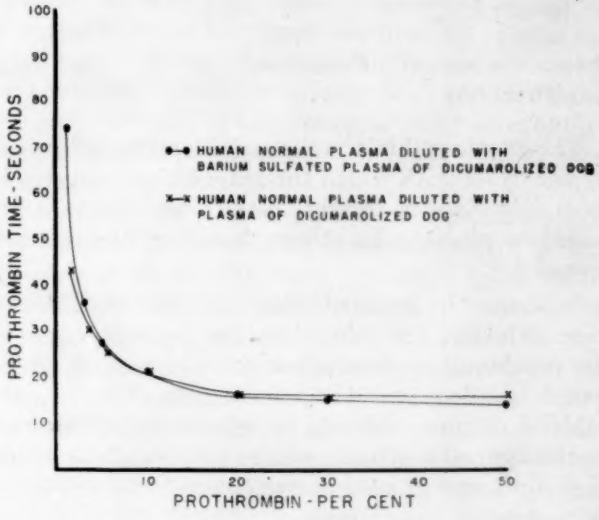
PROTHROMBIN TIME - SECONDS
PROTHROMBIN - PER CENT
HUMAN NORMAL PLASMA DILUTED WITH BARIUM SULFATED PLASMA OF DICUMAROLIZED DOG
HUMAN NORMAL PLASMA DILUTED WITH PLASMA OF DICUMAROLIZED DOG

FIGURE 2. *Comparative Effects of Dicumarol and Barium Sulfate on Plasma in Relation to Its Use as Diluent in the Determination of Prothrombin.*

The dog received a total of 18.7 mg. of dicumarol per kilogram of body weight intramuscularly for twelve days before the experiment. The prothrombic activity of the plasma, which was used as diluent, was 0.5 per cent.

prothrombin-free rabbit plasma. It is not clear whether this is due to the presence in these species of an as yet unknown factor not present in man or to larger amounts of known nonprothrombin clotting factors that influence prothrombic activity.‡ If the latter were true, barium sulfate dog or rabbit plasma might be preferable as a diluent in the one-stage procedure, since excesses of these factors might thus be assured.

Some investigators have used plasmas rendered prothrombin free in other ways — namely, by ad-

*Barium sulfate is said to remove approximately 50 per cent of Factor V from plasma, but how much is required to do this is not reported.[3]

†It should be mentioned that recent evidence suggests that dicumarol affects the clotting system of plasma in more ways than mere reduction in prothrombin.[38] If this is so, it is noteworthy that barium sulfate has the same effect.

‡Quick and Stefanini[16] have found that more labile factor is present in dog plasma than in human plasma.

sorption with aluminum hydroxide,[6, 41] with tricalcium phosphate[17] or by passage through Seitz filters.[3] Before these procedures can be evaluated one should know whether or not they also affect the nonprothrombin-clotting components.

The preparation of barium sulfate plasma requires complete separation of the adsorbing agent since residual traces may affect, by continued adsorption, the prothrombin of the test plasma that is diluted.[42] This probably holds true also when other adsorbing agents are used.

It should be remembered, furthermore, that the labile factor is at least just as labile in prothrombin-free as in whole plasma. Accordingly, the deprothrombinated plasma should be used shortly after preparation. We have found barium sulfate plasma fully potent for at least five hours if it is kept refrigerated.

Other Important Variations in the One-Stage Procedure

The prothrombin time is considerably influenced by the order with which the reagents are mixed. In most laboratories thromboplastin and calcium are added *to plasma*. In others, however, the order is reversed.[43]

It should be pointed out also that 0.02M calcium chloride, the concentration generally used in the prothrombin determination, has recently been found inadequate for dicumarolized plasma[29]; 0.025M calcium chloride is recommended instead. In the light of this finding older studies of the effects of dicumarol will need re-evaluation.

Two-Stage Method

General Procedure

The two-stage technic is based upon *complete* conversion of prothrombin to thrombin by thromboplastin plus calcium. The yield of thrombin is subsequently measured. By definition, 1 unit of prothrombin gives 1 unit of thrombin; and 1 unit of thrombin is that amount which will clot 1 cc. of a standard fibrinogen solution in fifteen seconds at 28°C.[8]

In the determination the test plasma is defibrinated by the addition of a small amount of thrombin, excesses of which are inactivated by incubation. The mixture is then diluted serially with saline solution, the dilutions are treated with thromboplastin and calcium, and the resultant mixtures allowed to stand until conversion of prothrombin to thrombin is complete. They are then reacted with a solution of fibrinogen. A sample of the dilution that induces coagulation in fifteen seconds is considered to contain 1 unit of thrombin. From the dilution the concentration of thrombin (in units), or its precursor, prothrombin, is computed.

Weaknesses and Limitations

Antithrombin. Perhaps the most serious limitation of the two-stage procedure is in the determination of plasma prothrombin when its concentration is low. With relatively normal prothrombin levels the method calls for high dilution of the plasma. Hypoprothrombinemic plasma, however, must be diluted *less* than normal plasma to furnish a mixture that will yield sufficient thrombin to clot the standard fibrinogen solution in the required time. Because of this, thrombin inactivation by antithrombin may become formidable, leading to gross inaccuracies. The lower the prothrombin, the greater the question of antithrombic activity looms. For clinical purposes, where interest is focused largely on hypoprothrombic conditions, this drawback makes the procedure of limited value. A method to circumvent antithrombic activity has been reported,[44] but experience with it has been limited.

Importance of nonprothrombin factors affecting the evolution of thrombin. In the two-stage procedure *complete* conversion of prothrombin and measurement of the evolved thrombin is assumed *before* the influence of antithrombin supervenes. As mentioned above, Ware and Seegers[4] have shown that prothrombin conversion is both retarded and incomplete when accelerator globulin is decreased or absent. This may occur under certain pathologic conditions in which hypoprothrombinemia has also been observed.[18] The serious effect of antithrombin when thrombin evolution is slow has already been discussed. Seegers et al.[18, 45] have accordingly modified the two-stage method by providing supplements of accelerator globulin.

Other factors have recently been described (Factor V of Owren[3] and labile factor[2]), which similarly accelerate the conversion of prothrombin to thrombin. The question arises whether they too should be provided to a test plasma to assure complete as well as rapid prothrombin conversion. Since none of them are available commercially, they would have to be prepared independently — a laborious task. Otherwise, deprothrombinated plasma must be added to the prothrombin-thromboplastin-calcium reaction mixture, a procedure not unlike the dilution technic of the one-stage method. This would introduce the untoward effects of antithrombin.

Serum prothrombin. These considerations bear significantly on the two-stage determination of serum prothrombin. As pointed out above, serum not only is devoid of fibrinogen but also frequently contains suboptimal amounts of labile factor.[21] Furthermore, accelerator globulin is relatively unstable in human serum.[45]

Also to be considered is evidence indicating that thrombin is capable of destroying prothrombin.[46] It will be recalled that in the two-stage procedure the test plasma is first defibrinated by additions of

thrombin. In serum, also, thrombin has been evolved as a consequence of coagulation. To what extent this clotting agent, added or spontaneously elaborated, affects the prothrombin in question requires further elucidation.

Laboriousness of the two-stage technic. Practically all investigators agree that the two-stage technic is much more laborious than the one-stage procedure. This precludes its routine use in most clinical laboratories.

Aims and Orientation of the Physician

The physician who requests a prothrombin determination should have a clear idea of the information he seeks. Does he want to know the precise concentration of this factor in contradistinction to other clotting constituents? Or does he seek an over-all appraisal of the ability of the plasma to evolve thrombin, which may help him detect a more general coagulation defect underlying a hemorrhagic disorder? And, above all, the physician prescribing dicumarol for the prevention or treatment of thromboembolic disease wants to know the effective, yet safe, "prothrombin level," whether his patient is within that range, and how he can be kept there consistently. It should be emphasized that one who undertakes anticoagulant therapy tampers with one of the most important homeostatic functions of the body, and that dicumarol strikes at the keystone in the mosaic of the blood clotting mechanism.

And how should the physician interpret the results reported by the laboratory? Considerable confusion exists in the minds of practitioners regarding the terms "prothrombin per cent," "prothrombin time," "normal control," "diluted prothrombin time," "prothrombin activity" and "clotting time" and their relations to each other.

Confusion would be avoided if a sound and simple modification of the two-stage procedure were available since with this technic quantitation is in terms of clearly defined units. For various reasons, some of them discussed above, this procedure is employed in very few clinical laboratories.

At the risk of repetition the above terms are reconsidered. "Prothrombin time" is an empiric interval representing the minimal time required for oxalated or citrated plasma to clot when provided with optimal amounts of thromboplastin and calcium. Practically speaking, it bears no relation to the clotting time of whole blood, or to the clotting time of recalcified plasma (recalcification time). In normal subjects it may be between 12 and 14 or more seconds, depending upon individual variation in prothrombic activity and upon the thromboplastin preparation used in the determination.

"Prothrombin concentration" refers to the actual level of prothrombin in the plasma, and is expressed in percentage ("prothrombin per cent") of what is found in normal subjects.* This must be distinguished from "prothrombin activity," or, as we propose, "prothrom*bic* activity," which indicates the over-all ability of plasma to form thrombin in the presence of optimal thromboplastin and calcium, reflecting the activities not only of prothrombin but also of nonprothrombin clotting factors.

Prothrombic activity, also expressed in percentage of normal, is calculated by interpolation of the observed prothrombin time on a standardization curve, that relates prothrombin time with various degrees of dilution of normal plasma. Different curves are obtained with different diluents. The advantage as diluent of prothrombin free, yet otherwise normal, plasma is that it assures normal amounts of nonprothrombin clotting factors, thus permitting determination of actual prothrombin concentration. The prothrombin concentration of a test plasma can be computed from the prothrombin time observed on the plasma similarly diluted with the prothrombin free plasma. As far as we can determine, barium sulfate plasma approaches the ideal diluent most closely.

Lowering the concentration of prothrombin or various plasma clotting components results in little increase in the prothrombin time until prothrombic activity is about 25 per cent of that found in the average normal subject. The difference in prothrombin time between plasma containing 50 per cent of normal prothrombic activity and 100+ per cent is practically within the limits of accuracy of the measurement. Accordingly, reports of prothrombic activity (as determined on *whole* plasma) in this range have little significance except to indicate that the activity is above 50 per cent.

Determinations on diluted plasma ("diluted prothrombin time") are more precise and are especially useful in the range of prothrombic activity exceeding 15 per cent of normal. Below this, little is gained by this modification, since sufficient accuracy is obtained by determining the prothrombic activity on whole plasma. If, however, information is desired concerning the concentration of prothrombin itself rather than of its activity in conjunction with nonprothrombin factors that also affect the prothrombin time, dilution with prothrombin free (yet otherwise normal) plasma offers distinct advantages.

It is important to recognize the wide variation in the prothrombic activity of normal persons. The "control value," obtained on one normal subject and reported side by side with the value given for a test plasma, serves merely to indicate the potency of the thromboplastin reagent used, and by no means as a basis for strict comparison.

Experience indicates that when prothrombic activity exceeds 20 per cent of normal, hemorrhage is rarely, if ever, due to deficiency of prothrombin, its activators or fibrinogen. This degree of hypo-

*In the two-stage technic prothrombin concentration is expressed in units. Normal human plasma is said to contain 300 units per cubic centimeter.

prothrombic activity can be readily detected by measurements on undiluted plasma.

Frequently it may be desirable to determine whether the clotting defect is due to low prothrombin per se or to inadequacy of the other factors belonging to the prothrombin constellation.* This can be done by simultaneous determinations with the nonprothrombin factors provided (by diluting with prothrombin-free normal plasma) and without providing these factors (by determining prothrombin on the undiluted plasma). If low activity is due to deficiency of prothrombin alone the results will agree closely. If, however, the low activity is referable to nonprothrombin factors, the value obtained by the dilution technic will be higher (after correction for dilution) than that obtained on undiluted plasma.

The estimation of prothrombic activity in the patient who is about to receive, or is receiving, dicumarol deserves special consideration. The drug apparently acts by blocking prothrombin synthesis in the liver. The goal of therapy is reduction of circulating prothrombin to a level where intravascular clotting is prevented or stopped, but not to the point where hemorrhage is likely to ensue. Obviously, a delicate balance must be attained between the velocity with which prothrombin disappears from the blood after its formation is blocked and the speed with which it is regenerated when the drug is eliminated.

*For the purposes of this paper fibrinogen is included in this constellation.

It has been repeatedly observed that the prothrombin time of dicumarolized subjects fluctuates sharply. Many of the reasons for this are clear. In a dog that receives a large dose of the drug about 80 per cent of the plasma prothrombin disappears within twenty-four hours (Fig. 3). The remaining 20 per cent is still sufficient to give a relatively normal prothrombin time since the difference in prothrombin time between plasma with 100 per cent prothrombin and that with 20 per cent is only slight (Fig. 1). During the next ten hours the prothrombin continues to decline precipitously and reaches sufficiently low levels to give markedly elevated prothrombin times.

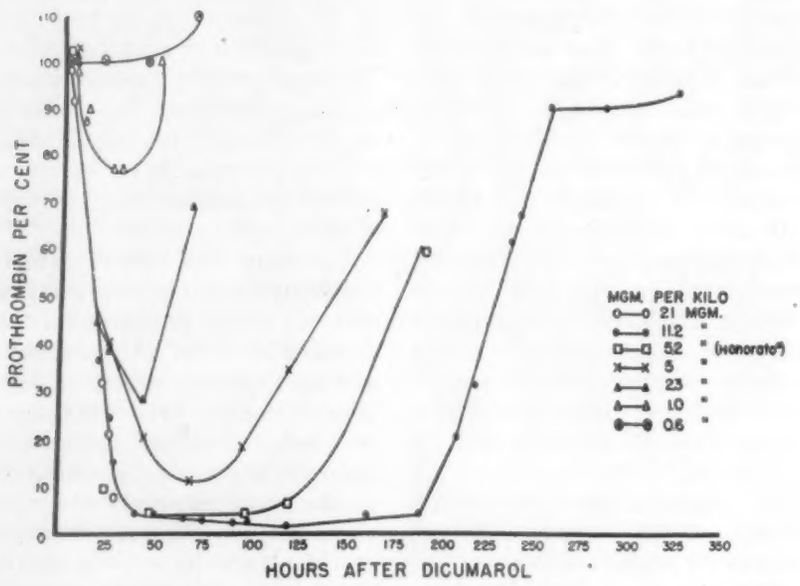

FIGURE 3. *Effect of Varying Doses of Dicumarol on the Plasma Prothrombin Concentration in the Dog.*

All observations, with the exception of those of Honorato,[12] *were obtained on the same animal. Dicumarol was administered intramuscularly as a suspension in propylene glycol.*

If dicumarol had been given to an animal with a prothrombic activity of only 30 per cent or less (of normal), the drug would have induced an elevated prothrombin time within a much shorter interval. Since determinations by the orthodox technic could hardly have distinguished with certainty between 30 per cent prothrombin and 100 per cent the quicker effect might have been attributed to undue sensitivity to the drug. This indicates the importance of knowing prothrombic activity precisely before dicumarol administration.

The regeneration of prothrombin when the effects of dicumarol are wearing off is equally rapid (Fig. 3). An elevated prothrombin time can return very quickly to a relatively normal one without necessarily indicating restoration of 100 per cent of the

prothrombic activity. If to these considerations are added differences in the weights of patients,* possible variations in rate of absorption† of the drug from the intestinal tract, and individual variations in liver function or other bodily functions controlling prothrombin synthesis and dicumarol elimination,‡ one can readily understand the wide and sharp fluctuations in plasma prothrombic activity often observed during dicumarol therapy.

The conclusion appears inescapable that the best guide to dicumarol therapy is frequent and precise determinations of prothrombic activity as well as prothrombin concentration. In the range of 15 to 100+ per cent of prothrombin (12-second to 16-second prothrombin time) precision can best be attained by the use of a proper dilution technic.

It is difficult to state what concentration of prothrombin is both "safe" and effective in prevention or treatment of thromboembolism. The literature is replete with recommendations that a prothrombin time of between 30 and 40 seconds, or that a level of 20 per cent of prothrombin, should be maintained. While experience indicates that a prothrombin time of 30 to 40 seconds is safe in persons with otherwise normal hemostatic function, it may be hazardous in the presence of other disturbances in the hemostatic mechanism. Furthermore, such a prothrombin time has little significance unless the potency of the thromboplastin used is known from prior standardization on normal subjects. Also, many of the reports recommending a prothrombin concentration of 20 per cent are based upon saline dilution curves. In the light of the advances made in the determination of prothrombin this figure is no longer tenable.

In our experience a prothrombin concentration of between 5 and 10 per cent of normal (obtained by the procedure outlined below) can usually be regarded as safe. Also, at this level coagulation is defective.[24] How effective this is against thrombotic disorders requires further clinical observation.

Recommended Procedure for Prothrombin Determination

The method that we consider at the present time most satisfactory for general clinical use in the determination of prothrombin is outlined in detail. The technic is essentially the one-stage method of Quick as modified by Rosenfield and Tuft.[37]

Thromboplastin extract (prepared from Difco thromboplastin[46]) is pipetted in 0.1-cc. amounts into each of many prothrombin-time test tubes, which are then stored at −10°C. until used. The extract thus stored in the frozen state in ready-to-use units retains its potency for as long as seven months.[46] To standardize it, prothrombin times on a plasma pool from at least 5 normal subjects are determined with each batch according to the following technic:

Barium sulfate plasma.§ To each cubic centimeter of fresh normal plasma is added 0.1 gm. of powdered barium sulfate (C.P.). The mixture is shaken, placed in the incubator at 37°C. for fifteen minutes, during which it is shaken frequently, and then centrifuged for thirty minutes at 3000 r.p.m., after which the supernatant is carefully separated. This barium sulfate plasma, used as the diluent, should be kept at refrigerator temperature (4–5°C.) and should be used within five hours of preparation.

Standardization curve. Various dilutions are made of the pooled normal plasma with the barium sulfate plasma; 0.10 cc. of each of the dilutions is added to a thromboplastin tube that has been thawed for ten minutes in the water bath at 37°C., 0.10 cc. of 0.025 M calcium chloride is squirted in from a tuberculin syringe, and the time of clotting observed while the mixture is constantly agitated with a wire loop. The standardization curve relating the prothrombin time with the prothrombin concentration in percentage is obtained by plotting the observed prothrombin times against the percentage of normal plasma in the normal plasma-barium-sulfate plasma mixtures.

Determination of prothrombin concentration of the test plasma. Of the test plasma 0.10 cc. is mixed with 0.90 cc. of fresh (no more than five hours old) normal plasma treated with barium sulfate as described above; 0.1 cc. of the mixture is added to a thromboplastin tube, and calcium chloride solution added as described above. From the observed prothrombin time of the mixture, the percentage prothrombin is interpolated from the standardization curve. This value, multiplied by 10 to correct for the 1:10 dilution, gives the prothrombin concentration of the undiluted plasma in percentage of normal.

For extremely hypoprothrombinemic plasma a smaller dilution may be necessary (0.4 cc. of test plasma to 0.6 cc. of barium sulfate plasma). Under such conditions the appropriate dilution correction must be made.

Determination of prothrombic activity. In the determination of prothrombic activity on undiluted plasma, the procedure is the same, omitting dilution with barium sulfate plasma. The results are similarly interpolated from the standardization curve described above, and are expressed as prothrombic activity in percentage of normal.

Determination of serum prothrombic activity. To 0.7 cc. of barium sulfate normal plasma 0.3 cc. of oxalated serum, incubated at 37°C. for half an

*Note in Figure 3 the differences in degree and duration of dicumarol action in relation to size of dose per kilogram of body weight.

†In man, dicumarol is given exclusively by the oral route.

‡Little is known regarding prothrombin synthesis or dicumarol elimination, both of which can conceivably be greatly influenced by the underlying disease or its complications.

§All plasmas are from blood oxalated with 1 cc. of 0.1M sodium oxalate to 9 cc. of blood.

hour to inactivate thrombin, is added. The prothrombin time is determined on 0.1 cc. of the mixture in the usual manner, the result interpolated from the standard curve, and the dilution correction applied.

Summary

The available methods for determination of plasma prothrombin are scrutinized in the light of recent advances in knowledge of prothrombin, its activators and accelerators, and its role in the coagulation of blood. Since several nonprothrombin components as well as prothrombin have a profound effect on the velocity of thrombin evolution from prothrombin or on the amount formed and available for clotting fibrinogen, great caution must be exercised in drawing conclusions regarding actual prothrombin concentrations from one-stage prothrombin times or from two-stage prothrombin determinations.

Other weaknesses and limitations of prothrombin methods are discussed, the aims and orientation of the physician are considered, and the most satisfactory clinical laboratory method for prothrombin determination is described.

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PARTIAL URETERAL OBSTRUCTION*

Its Effect on Urinary Excretion

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A PATIENT with a unilateral ureteral stricture afforded an unusual opportunity to observe the effects of partial obstruction on urinary excretion and the changes in excretion subsequent to its relief. The stricture followed a ureterolithotomy done in the presence of marked infection of the ureter and kidney above the level of the obstructing calculus. A brief report of this case follows.

W. S. D., a 49-year-old white salesman, was admitted to the West Roxbury Veterans Hospital in October, 1947, for the third time with symptoms of frequency, nocturia and a persistent dull ache in the right flank.

This illness had begun 2½ years previously, when he had been studied at this hospital for total hematuria of 3 days' duration. The hematuria had subsided at the time of entry to the hospital. An x-ray film of the abdomen had revealed several opacities in the region of the right kidney, but the patient had refused further investigation and had been discharged without a complete study.

In March, 1947, he was admitted to the hospital for the second time. There had been no major urinary symptoms during the 2 years between the first and second admissions. At this second admission he complained of severe pain in the right flank of several days' duration. He was acutely ill and had marked tenderness in the right costovertebral angle. Studies revealed a semiopaque calculus in the upper right ureter. At operation a stone located approximately 8 cm. below the ureteropelvic junction was removed. Because of marked infection of the ureter, T-tube drainage of the ureter and kidney was instituted. The tube was removed 2 weeks later; after several days of urinary leakage, the wound became dry and healed, and the patient was discharged in June, 1947. On analysis the calculus was found to be of the mixed type.

The third admission occurred approximately 6 months after the ureterolithotomy with drainage. In the interim he had been fairly well but had recently noted a loss of energy, some burning on urination, frequency and nocturia. There had been no episodes of fever or acute pain in the right flank.

Physical examination showed that the patient was not in acute distress. There was a well healed, right subcostal scar. There was no costovertebral-angle tenderness. The voided urine was cloudy and contained numerous pus cells. There was no residual bladder urine. Retrograde ureteral catheterization revealed an impassable obstruction in the right ureter at the level of the previous surgical incision. There was considerable hydronephrosis and hydroureter above.

The temperature and pulse were normal, and the blood pressure was 145/95.

Studies of the blood showed a calcium of 10.2 mg., phosphorus of 2.8 mg., uric acid of 3.9 mg. and total protein of 7.33 gm. per 100 cc. The alkaline phosphatase was 2.0 Bodansky units. A culture of the bladder urine showed the presence of *Aerobacter aerogenes*.

TABLE 1. *Preoperative Study.*

KIDNEY	URIC ACID	PHOSPHORUS	CALCIUM	pH	PHENOLSULFONEPHTHALEIN		CULTURE
					APPEARANCE TIME	QUANTITATIVE TEST	
	mg./100 cc.	*mg./100 cc.*	*mg./100 cc.*		*min*	*mg./cc.*	
Right	12.0	16.1	21.9	7.5	0	0	*A. aerogenes*
Left	26.0	69.0	20.5	6.9	3	0.05	Sterile

On November 14 the right upper ureter was explored. The ureter was imbedded in extensive scar tissue, and approximately 8 cm. below the ureteropelvic junction there was a dense stricture, which did not admit the tip of a small duct probe. The ureter above was moderately dilated. A small segment of ureter containing the stricture was excised, and an end-to-end anastomosis performed over the upper arm of a T-tube, which was brought out at the lower angle of the incision. The tube was removed 6 weeks after operation. The fistulous tract healed rapidly, without urinary leakage, and the patient was discharged in December, free of symptoms.

Before the second operation studies were made of the urinary excretion from each kidney. An open-ended No. 6 Fr. catheter was passed up each ureter. These were used so as to tamponade the ureteral walls and thereby direct the entire volume of urine through the collecting catheters. The left catheter was passed to the renal pelvis. There was obstruction to the passage of the right catheter at the level of the stricture, and the tip of the instrument appeared to have fixed itself within the stricture site. The flow from both catheters was free and abundant. Specimens were collected in test tubes of equal size. By observation of the levels of urine in each test tube at regular intervals, it was noted that

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approximately equal quantities of urine were being excreted by each kidney. By such a rough estimation it was assumed that the volume excretion per minute of the affected right kidney closely paralleled that of its normal mate. The amounts of uric acid, calcium, phosphorus and phenolsulfonephthalein were determined. There was a distinct difference in the quantities of these substances excreted in the urine from the right and left kidneys. The results of the analysis of each specimen are given in Table 1. Values are recorded in milligrams per 100 cc. The quantitative phenolsulfonephthalein is given in milligrams per cubic centimeter.

FIGURE 1. *Intravenous Urogram Taken before Ureteroplasty.*

It is interesting to note that the chemical values recorded for the affected right kidney were strikingly lower than those for the normal left kidney, even though the volume of urine excreted was the same. The only exception was the quantity for calcium, which was even a fraction higher than that on the left.

Six months after the plastic repair of the right ureter these studies were repeated. In addition an intravenous urogram taken before operation (Fig. 1) was compared with a direct pyelogram taken 5 weeks after operation (Fig. 2). Films taken 6 months after ureteroplasty demonstrated more rapid excretion and a better concentration of the dye in the right kidney (Fig. 3).

Postoperatively, both urine specimens were collected from the renal pelves, since there was no further obstruction to the passage of the No. 6 Fr. catheter up the right ureter. The values obtained showed a more normal relation between the urine excreted from the right and that from the left kidney (Table 2).

It will be noted from Table 2 that the postoperative values recorded for the affected right kidney more closely approximated those for the normal left. Particularly striking were the figures for phenolsulfonephthalein appearance time and quantitative phenolsulfonephthalein. Previously, these values had been zero on the right.

The same studies were made on a control subject with a normal upper urinary tract. The patient was a young man who had been admitted to the hospital for investigation of long-standing enuresis. Individual urine specimens were obtained from him during the course of the examination. Blood chemical values were within normal limits throughout. The several values recorded for each kidney of a normal control subject closely paralleled one another. The figures for each kidney are given in Table 3.

DISCUSSION

Final conclusions cannot be drawn from observations on a single case. However, the findings in this case suggest several points of interest when compared with the results of studies made by others. The excretion of normal urine is directly dependent upon the functional integrity of the tubular system. Hayman[1] and Gamble[2] state that the excretion of phenolsulfonephthalein and diodrast appears to be primarily a function of the tubules. Of the amounts given for functional tests approximately 90 per cent of both phenolsulfonephthalein and diodrast is excreted by the tubular system, and only 10 per cent passes through as glomerular filtrate. When given in test doses the bulk of phenolsulfonephthalein and diodrast is bound by adsorption to the plasma proteins. Because of this link, tubular activity is required to effect a separation and excretion of these plasma-bound substances. In the case presented

FIGURE 2. *Direct Pyelogram Taken Five Weeks after Operation.*

above, the fact that preoperatively no phenolsulfonephthalein and very little diodrast were excreted by the affected kidney suggests a greatly altered tubular physiology. The probable cause for this altered function was an increased intrapelvic pressure secondary to partial ureteral obstruction. That this sequence of events — obstruction, back pressure and tubular dysfunction — had occurred is further supported by the successful attempt at restoration of normal tubular function during the six months following operation for relief of the obstruction. This is brought out by comparison of the respective values given in Table 1 and 2. Hinman,[3] in his studies on hydronephrosis, has clearly demonstrated the structural changes in the tubules that follow hydronephrosis secondary to complete or partial urinary obstruction. The concomitant and subsequent functional change was shown to be one of gradual dilution and diminution of total volume of urine excreted.

Another observation worthy of note is the variation in the calcium level in the preoperative and postoperative study. Urinary stasis, secondary to obstruction of whatever type, has long been recognized and accepted as a definite predisposing factor in the formation and in the recurrence of renal calculi. Higgins,[4] in discussing factors in the recurrence of renal calculi, noted that many recurrences followed a previous ureterolithotomy. Of these, a significant percentage of cases showed a secondary stricture at the operative site. Rolnick and Singer,[5] working with dogs in a study of the effects of overdistention of the renal pelvis and ureter, demonstrated the structural damage that can occur to both medulla and cortex with various degrees of increased intrapelvic pressure. They noted also that in the urine from a blocked kidney there was a distinct diminution of the chloride content and an increase in the urea content as compared with the unobstructed side. Since the majority of calculi contain calcium to a greater or lesser degree, the urinary excretion of this element is of particular interest. A stone-forming kidney probably excretes a greater amount of calcium salts than a normal one. Flocks,[6] in 1939, reported analyses of individual urine specimens taken from "stone-bearing" kidneys and their normal mates. Values for urinary calcium were found to be greater in the stone-forming kidneys. Furthermore, the study revealed that a slight pathologic change in the kidney was usually associated with an increased urinary calcium; a lowered calcium output was noted in kidneys with marked pathologic changes. This observation suggests that stone-forming tendencies are greater early in the course of disease of the tubular system than in the irreversible or decompensated stage. Hunner,[7] in 1924, noted the frequency of ureteral calculi in cases with proved ureteral stricture. In a later paper he[8] emphasized the role of urinary stasis as a major etiologic factor in calculi in the upper urinary tract.

FIGURE 3. *Urogram Taken Six Months after Operation.*

TABLE 2. *Postoperative Study.*

KIDNEY	URIC ACID	PHOSPHORUS	CALCIUM	pH	PHENOLSULFONEPHTHALEIN		CULTURE
					APPEARANCE TIME	QUANTITATIVE TEST	
	mg./100 cc.	*mg./100 cc.*	*mg./100 cc.*		*min.*	*mg./cc.*	
Right	7.5	20.8	8.82	6.8	4½	0.0214	*A. aerogenes*
Left	6.5	36.7	9.31	5.6	3½	0.0425	*A. aerogenes*

In the majority of studies, attention has been directed to local conditions as possible causes of renal stones, but consideration must be given to systemic conditions as well. The frequent occurrence of uric acid, and occasionally cystine stones, indicates something other than local factors in such patients. Al-

bright et al.,[9] in an extensive study on hyperparathyroidism, clearly showed the direct relation of this systemic disease to frequent and recurrent formation of renal calculi in patients with surgically proved parathyroid tumors or hyperplasia. The systemic disturbance in the metabolism of calcium and phosphorus results in an increased excretion of these elements in the urine. A calculous nidus in the kidney, being constantly bathed in a highly concentrated solution of these substances, will have ideal conditions for the gradual formation of a calculus. Such patients usually exhibit bilateral stones either concurrently or alternately.

In most patients the formation of unilateral recurrent calculi cannot be explained on the basis of systemic disease alone. In these patients, who show no evidence of systemic disease, local factors appear to be responsible for the calculi. The exact mechanism of the process is obscure. Of the many recognized entities, urinary stasis and back pressure seem to be highly significant ones. In a decompensating or decompensated kidney, resulting from back pressure, the tubular physiology is greatly altered. In the case reported above, there was definite evidence of disturbed tubular function as shown by the failure of the affected kidney to excrete phenolsulfonephthalein and diodrast preoperatively. Furthermore, the wide variation in the amounts of other substances excreted is further evidence of tubular dysfunction. Despite this apparent failure of the tubular system the amount of calcium excreted was slightly higher than that of its normal mate. These findings suggest the possible relation of abnormal tubular physiology to the formation of renal stones.

Another point brought out by this case study is that regarding the value of reconstructive surgery to conserve renal tissue. Dodson[10] has reported a large series of cases in which corrective surgery has resulted in the reconstruction of relatively good structural and functional kidneys. Because of the structural distortion and marked loss of function of the right kidney in the case presented, preoperatively, the probability of a nephrectomy was considered. The finding of a short, partially obstructing stricture at operation prompted the course of treatment employed. That this procedure was justified is evidenced by the structural and functional improvement of the affected kidney in the six months following operation.

Table 3. *Control Study.*

Kidney	Uric Acid	Phosphorus	Calcium	pH	Phenolsulfonephthalein		Culture
					Appearance time	Quantitative test	
	mg./100 cc.	*mg./100 cc.*	*mg./100 cc.*		*min.*	*mg./cc.*	
Right	45.6	18	28.9	4.5	5	0.49	Sterile
Left	46.2	16.5	29.7	4.5	5	0.50	Sterile

Summary

A study on partial ureteral obstruction and its effect on urinary excretion is presented. Quantitative analyses of uric acid, phosphorus, calcium and phenolsulfonephthalein in the urine specimens from a partially obstructed kidney and its normal mate were made. It was found that there was a marked diminution in the excretion of all these elements except calcium in the urine from the affected kidney. This wide variation disappeared after relief of the obstruction. Inferences regarding altered tubular function and increased tendency to stone formation are drawn from the data presented. Early recognition and treatment of obstructing lesions of the urinary tract may obviate the subsequent occurrence of a more serious disease.

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MUMPS COMPLICATED BY MYOCARDITIS, MENINGOENCEPHALITIS AND PANCREATITIS

Review of the Literature and Report of a Case

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MUMPS is usually considered to be an acute systemic disease of specific viral etiology with a special predilection for the parotid glands. The common complications are orchitis, pancreatitis, oöphoritis, mastitis and meningitis or meningoencephalitis, or both. Myocarditis has until the past few years been considered a rare and unusual complication. Several studies recently made call attention to the occurrence of myocarditis during the convalescent course of epidemic parotitis.

It is the purpose of this paper to submit a case report as additional evidence to support the belief that mumps is a generalized infectious process and that the myocardium and pericardium may be involved by an acute, infectious process of viral etiology; such affections may occur with varying frequency and may be of any varying severity. A discussion of the importance and implications of the studies made in the past few years is offered.

Pujol[1] first suggested in 1918 that myocarditis might be a complication of mumps. He reported 3 cases, each of which manifested clinical evidence of myocardial involvement; however, he lacked electrocardiographic confirmation. In 1925 Barbato[2] suspected mumps myocarditis on the basis of clinical observation. Manca,[3] in 1932, was the first to report pathological sections in a case of acute, interstitial, fibrinous myocarditis occurring in a fatal case of mumps. He believed that this was a typical tissue reaction to the mumps virus. Wesselhoeft[4] reviewed progress in mumps in 1942 and at that time noted the evidence of its being a systemic disease with a predilection for certain tissues. He remarked on the frequency with which clinical and subclinical mumps meningoencephalitis was unrecognized. The complement-fixation test for mumps virus on cerebrospinal fluid or blood serum and the dermatologic sensitivity test of Enders and his coworkers[5] were discussed. Wendkos and Noll,[6] in 1944, reported a case of mumps myocarditis diagnosed only by a chance electrocardiogram. They noted minor T-wave changes, bradycardia and lengthened PR interval, which was clearly temporarily shortened by atropine as is first-degree heart block secondary to active rheumatic carditis. Rosenberg[7, 8] reported an epidemic study in which electrocardiographic evidence of cardiac involvement was noted in 16 of 104 cases of mumps, or 15.4 per cent. Changes in the tracings (done serially) all occurred between the fifth and tenth days of illness, and returned to normal in from two to thirty-five days. Only 4 of the 16 patients had clinical evidence of cardiac involvement. Seven of the 16 had acute orchitis as a complication. This author points out how the implications reached pertain to rheumatic fever. He suggests that in the majority of cases mumps myocarditis follows a subclinical course and requires electrocardiographic studies for its recognition. He noted changes of varying magnitude in all complexes, but no specific pattern was noted. Felknor and Pullen[9] added another case with clinical and electrocardiographic evidence of myocarditis. There are many reports, such as that of Holden, Eagles and Stevens,[10] describing central-nervous-system involvement in mumps. Bruenn[11] has reported on the mechanism of impaired auriculoventricular conduction in acute rheumatic fever, and Keith[12] studied overstimulation of the vagus nerve in rheumatic fever, emphasizing the nonspecific nature of PR-interval prolongation. Saphir[13] reported myocarditis in bronchiectasis and noted the discrepancy between pulse rate and a slight elevation of temperature. The PR interval has been reported prolonged in other acute infectious diseases such as pneumonia, scarlet fever, diphtheria and measles.

The following case is reported as an instance of a complication of mumps and as additional evidence that the infection is a generalized disease.

CASE REPORT

J. H., a 55-year-old man, was admitted to the hospital on June 2, 1947, with a history of epigastric discomfort and a sense of expanding pressure, high in the epigastrium, of 2 days' duration. This was exaggerated by effort, but was described as "indigestion." In about 2 hours marked nausea, vomiting and extreme weakness, which lasted 48 hours, followed. The patient vomited or retched every 15 or 20 minutes during this time. On the first night of the illness he was unable to lie flat in bed because of a choking sensation and dyspnea, relieved by sitting up on the edge of the bed. He complained of marked apprehension. Two episodes of syncope of 1 or 2 minutes' duration occurred on the day of admission. (This had never happened before.) He had chilly sensations and reported that he had a temperature of 102°F. He came to the hospital because of the dyspnea, which interfered with his work as a refrigerator repairman. On the day of admission, he developed a severe pulsating headache, located in the vertex, which continued for 5 days and finally subsided spontaneously. The patient was very lethargic and mildly disoriented. Marked anorexia was present for many days.

A careful review of the systems was not helpful. The past medical history disclosed nothing significant, and the family

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history revealed only that a sister had died of pulmonary tuberculosis in 1912. The patient was not a heavy smoker and did not drink inordinately.

Physical examination disclosed a middle-aged man lying quietly in bed. He was moderately apprehensive. There was mild bulbar conjunctival injection. The peripheral vessels were tortuous, but not difficult to compress. The ocular fundi showed Grade I arteriolosclerosis. The neck was supple. The chest was of an emphysematous type and the lung fields were clear. The heart sounds were very distant and difficult to hear. An arrhythmia was present that was interpreted as representing premature beats. The point of maximum impulse could not be palpated. No murmurs were heard. The abdomen was normal except for marked deep epigastric tenderness, pressure causing the lethargic patient to cry out. Peristalsis was readily heard. The extremities were normal. Neurologic examination was negative except for mild disorientation.

The temperature was 102°F., the pulse rate 64, and the respirations 22; the blood pressure in both arms was 120/78.

Examination of the blood disclosed a red-cell count of 5,200,000, with a hemoglobin of 16.8 gm.; and a white-cell count of 4200, with 61 per cent neutrophils and 39 per cent lymphocytes. Urinalysis was negative. The serum amylase was 14.7 units; the cephalin flocculation test was + in 24 and +++ in 48 hours. The sedimentation rate (Wintrobe method) was 8 mm. per hour. The blood urea nitrogen was 14.8 mg. per 100 cc. The cerebrospinal fluid contained 516 leukocytes per cubic millimeter, with 185 polymorphonuclear cells and 331 lymphocytes, a total protein of 63.3 mg., glucose of 63.3 mg. and chloride of 736.7 mg. per 100 cc.

A teleroentgenogram was normal, but electrocardiograms manifested a decreased voltage of the QRS complexes, frequent auricular premature beats and sinoauricular block with ventricular escape beats. The T wave in Lead 3 was of greater amplitude than that of Lead 1, which was considered probably abnormal, but the concomitant amplitude discrepancy in the QRS complexes of the same leads makes this equivocal. The very small R wave with a deep S wave in Lead CF_4 is also abnormal suggesting some myocardial disturbance in the lateral wall of the left ventricle.

The patient was treated with ordinary analgesics, and a tentative diagnosis was made of central-nervous-system viral infection of unknown type. Five days after admission a characteristic acute parotitis on the right, with swelling, tenderness and inflamed right parotid-duct orifice, rapidly developed. The serum amylase at this time was 22.4 units.

The subsequent course was uneventful, the temperature falling by lysis in 8 days, with a gradual disappearance of symptoms. Cerebrospinal-fluid studies later revealed a gradual return to normal limits. Cultures of blood and cerebrospinal fluid were repeatedly negative. Sixteen days later an electrocardiogram disclosed none of the conduction defects noted above, although the discrepancy in the T waves in Leads 1 and 3 and the absence of a normal R wave in Lead CF_4 persisted. The patient was discharged 37 days after admission, when he felt perfectly well. He was seen 6 months later and was still well, with no suggestion of sequelae.

Discussion

Unequivocal meningoencephalitis, as diagnosed by clinical and laboratory methods, was present in this case. A diagnosis of acute pancreatitis was thought justified in view of the sudden onset of violent nausea and vomiting persisting for forty-eight hours, the definite though subjective evidence of marked tenderness deep in the epigastrium and the sense of expanding epigastric pressure that did not radiate. The change in serum amylase may or may not have been significant. The patient had marked apprehension and orthopneic symptoms, which were followed by two episodes of sudden, unpredictable syncope with unconsciousness lasting one or two minutes; the electrocardiographic changes of decreased QRS complex, premature auricular contractions and ventricular escape suggested some interference with origin of the auricular impulse or poor auriculoventricular conduction. He also had dyspnea on the day of his admission while engaged in refrigerator-repair work, not a strenuous occupation. All this suggests imminent left-ventricle failure, as well as some degree of transient auriculoventricular or sinoauricular heart block. It was believed that these findings justified a diagnosis of myocarditis.

An etiologic diagnosis was not reached until the patient later developed acute right parotitis. Mumps can so readily explain the entire chain of events despite the unusual sequence that the patient was considered to have had the mumps virus, which had manifested its pathologic changes in the central nervous system, pancreas, heart and right parotid gland. The widespread distribution suggested blood-stream spread.

The case presented and the review of the literature strongly suggest that mumps myocarditis goes frequently unrecognized and usually manifests itself in a subclinical form. The importance of its recognition is that with the knowledge of its presence, one is more inclined to prolong the convalescence to prevent the occurrence of myocardial residua in the event of extensive involvement. Apparently, there are no residua, and the process is completely reversible in the vast majority of cases, though reversal may be delayed by failure to recognize its presence. It seems worth while to suggest the use of the complement-fixation test and the intradermal skin test of Enders,[5] as a diagnostic aid in an obscure myocarditis. The PR-interval changes discussed in the literature make the specificity of such changes in rheumatic fever a matter of conjecture. Wendkos and Noll[6] showed that the PR-interval prolongation of mumps myocarditis is shortened by atropine sulfate, as is the prolonged PR interval of acute rheumatic fever. The nonspecific nature of this electrocardiographic change should be appreciated. Though a PR interval may be within usual normal limits for the age of a patient, one should keep in mind that a tracing taken after recovery may show a much shorter PR interval, which is actually normal for the particular patient.

Rosenberg[7, 8] has stressed the fact that mumps myocarditis is probably not rare and has ably presented the implications of work done thus far and the importance of further study. Inasmuch as mumps is frequently not reported, a statistical study is difficult to accomplish and electrocardiographic study in all acute infectious diseases might well prove fruitful whenever such a program is feasible.

Summary

A case in which mumps was complicated by myocarditis, meningoencephalitis and pancreatitis is presented.

The literature on this subject is reviewed, and electrocardiographic study, when possible, is recommended in all infectious diseases.

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LEFT VOCAL-CORD PARALYSIS ASSOCIATED WITH HYPERTENSIVE HEART DISEASE

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LEFT vocal-cord paralysis is frequently observed in various forms of intrathoracic disease, such as aortic aneurysm, mediastinal tumors, pleuritic thickening and pulmonary tuberculosis. A variety of cardiac lesions, including mitral stenosis, arteriosclerotic heart disease, congenital heart disease and aneurysms of the large vessels, may also produce this syndrome. Its occurrence in only a small percentage of cardiac conditions is not clear.

Although a number of hypotheses have been proposed, the exact mechanism has not been elucidated. Ortner,[1] in 1897, first described vocal-cord paralysis associated with heart disease, his 2 cases occurring in mitral stenosis. At autopsy an enlarged auricle was reported to have caused compression of the recurrent laryngeal nerve against the aorta. In 1904 Alexander[2] was the first to advance the theory that the pulmonary artery by its own enlargement, or indirectly by enlargement of the left auricle, is pressed against the nerve and the arch of the aorta. Frischauer,[3] in 1905, found the nerve compressed between the aorta and left pulmonary artery by the pressure of a dilated left auricle and pulmonary vein. Fetterolf and Norris[4] (1911) reviewed 37 cases and, after careful anatomic studies of frozen specimens, concluded that dilatation of the left auricle caused the left pulmonary vein to press against the pulmonary artery, the latter in turn being forced against the aorta. It was their belief that the nerve paralysis was due to actual compression between the left pulmonary artery and aorta or ligamentum arteriosum. Kraus[5] suggested that in mitral stenosis the right ventricular dilatation caused a displacement of the heart to the right, with consequent dragging on the aortic ligament and resultant stretching and paralysis of the nerve. Guttman and Neuhof[6] observed that the nerve may also be compressed and incorporated between bands of pericardial and mediastinal adhesions; this occurred in a case of theirs in which pericarditis was present. Careful anatomic studies by Dolowitz and Lewis[7] demonstrated that the lymph nodes in the triangle formed by the pulmonary artery, aortic arch and ligamentum arteriosum might effectively compress the left recurrent laryngeal nerve when accompanied by cardiac hypertrophy or pulmonary-artery engorgement, or both. Other authors have suggested that the cicatrization occurring in sclerosis, thrombosis and atheromas of the pulmonary artery may be contributing factors. Emphasis has been placed upon dilatation of the pulmonary vessels, which may be apparent by fluoroscopy but may not be observed at autopsy.

The paralysis may occur at any time and is manifested by changes in the voice, which becomes hoarse and indistinct. The patient may be able to speak in a whisper. Laryngoscopy shows anything from a complete paralysis to sluggish movement of the vocal cord on the left side. The nerve is usually affected slowly by the gradual enlargement of the surrounding structures without marked accompanying cardiac symptoms, or it may be paralyzed rather suddenly during a sudden decompensation in a chronic case. Not infrequently there are relapses or recurrences of the paralysis of the left recurrent laryngeal nerve. In some cases the voice disturbance may be the first symptom that leads the patient to consult a physician. If the pressure has not been too severe or too prolonged, function will return with the removal of the cause. The prognosis in these cases is that of nerve injury from pressure in general.

Case Reports

Case 1. G. G. (A. H. 74076), a 61-year-old widowed sand blaster, came to the Outpatient Clinic of the Albany Hospital

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on May 5, 1948, with signs and symptoms of severe congestive failure. For 7 months prior to admission there had been progressive weakness, hoarseness, dyspnea, orthopnea, ankle edema, palpitation and precordial distress. During this time there were also episodes of left-sided chest pain, associated with a cough productive of small amounts of frothy blood-streaked sputum.

Aside from appendicitis and gonorrhea the past history was not significant. The family history was noncontributory.

Physical examination revealed the patient to be markedly dyspneic and orthopneic, with some cyanosis of the lips and nail beds. The fundi showed arteriovenous nicking and tortuosity and narrowing of the arteries. The neck veins were distended. Percussion of the chest revealed dullness over the left base posteriorly with absent breath sounds over this area. Moist rales were heard throughout both lung fields. On percussion the border of cardiac dullness extended to the left anterior axillary line, and the point of maximal impulse was located in the sixth intercostal space. The rhythm was totally irregular, and the sounds were of poor quality. No murmurs were heard. The abdomen was slightly distended, and the edge of the liver, which was firm and smooth, was palpated 4 cm. below the right costal margin. There was pitting edema of the lower extremities extending above the knees.

The temperature was 100.8°F., the pulse 106, and the respirations 28. The blood pressure was 250/140.

The urine was normal. Examination of the blood disclosed a hemoglobin of 14 gm., and a white-cell count of 12,000, with 94 per cent neutrophils. The fasting blood sugar was 123 mg., and the nonprotein nitrogen 46 mg. per 100 cc. The blood Wassermann reaction was negative.

A roentgenogram of the chest showed the heart to be enlarged. There was diminished transmission of rays through the left side of the chest, with displacement of the cardiac shadow to the right, suggesting effusion.

An electrocardiogram revealed auricular fibrillation and left-axis deviation, with left ventricular hypertrophy and strain. There was also evidence of myocardial damage.

A clinical diagnosis of hypertensive heart disease, with decompensation, auricular fibrillation and multiple pulmonary emboli with pleural effusion, was made.

The patient improved after treatment with bed rest, oxygen, diuretics, 1-gm. sodium diet, digitalis and dicumarol. Thoracentesis was performed twice, and neither the hemorrhagic pleural fluid nor the sputum showed tubercle bacilli or tumor cells.

On the 15th hospital day laryngoscopy demonstrated sluggish movement of the left vocal cord. As the patient continued to improve the heart decreased in size, and on the 31st hospital day he was discharged. His hoarseness had improved, and when he was seen again in the Medical Outpatient Clinic 3 months later it had cleared completely.

Case 2. M. S. (A. H. 48565), a 50-year-old housewife, came to the Albany Hospital for the first time on July 15, 1938, with signs and symptoms of severe congestive failure. For 6 months prior to admission there had been progressive dyspnea, ankle edema, orthopnea and weakness.

The past history was significant only in that she had had hypertension since her third pregnancy in 1931. The family history was noncontributory.

Physical examination showed the patient to be in severe congestive failure with a blood pressure of 240/120. After treatment and study a clinical diagnosis of hypertensive heart disease with decompensation and auricular fibrillation was made. She was discharged improved on the 20th hospital day to be followed in the Outpatient Clinic.

Since that first admission she has been hospitalized ten times for similar episodes of decompensation. Of particular interest has been the gradual increase in the size of the heart, which on x-ray study has shown an increase of 7 cm. within the past 4 years.

Hoarseness developed rather suddenly on October 11, 1945, and has persisted to date. Laryngoscopy showed complete paralysis of the left vocal cord. In view of the long-standing decompensation with marked cardiac enlargement the prognosis regarding the hoarseness is poor.

Discussion

These are 2 typical cases of vocal-cord paralysis associated with heart disease. When a patient with a cardiac lesion complains of hoarseness and laryngoscopy is confirmatory, paralysis of the left recurrent laryngeal nerve must be suspected as being due to pressure on the nerve. With the institution of proper therapy, if successful, the paralysis disappears. The condition in Case 1 responded satisfactorily to therapy; in Case 2 hoarseness appeared suddenly, and with the progressive cardiac hypertrophy and dilatation in spite of therapy, the paralysis is now complete and permanent.

Summary

Left vocal-cord paralysis is frequently observed with various forms of intrathoracic disease. A variety of cardiac lesions may also produce this syndrome. The theories of the mechanism involved are summarized.

Two cases of hypertensive heart disease with vocal-cord paralysis are presented.

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TORSION OF THE NORMAL FALLOPIAN TUBE COMPLICATING PREGNANCY*

Report of a Case

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BECAUSE torsion of the normal fallopian tube is a rare complication of pregnancy, the following case is added to those already on record.

Mrs. J. B., a 23-year-old primigravida, was admitted to the hospital on July 30, 1948. Eleven days previously she experienced her first attack of pain in the right anterior portion of the abdomen. This pain began without a known precipitating cause, had no localizing signs or symptoms and disappeared when the patient remained in the upright position for 20 minutes. After this episode and until 2 days before admission, the pain recurred daily, appearing occasionally in the right flank as well as in the right anterior portion of the abdomen. Three days before admission the patient noted intermittent urinary frequency. White cells were found in the sediment on microscopical examination of the urine. After a day without discomfort and on the day preceding admission the pain reached its maximum severity, and an area of right-lower-quadrant tenderness was noted for the first time.

The patient's last menstrual period had begun on February 6, and the estimated date of confinement was November 13. Except for morning sickness controlled by intravenous injections of thiamine hydrochloride and pyridoxine hydrochloride, the pregnancy had been uneventful. The past and family histories were noncontributory.

Examination of the blood disclosed a white-cell count of 11,600. Except for 28 per cent immature neutrophils, the differential count was normal.

Because of the urinary frequency and pyuria cystoscopy was done. There were no abnormal findings. After the cystoscopy, and because of the persistence of the right-lower-quadrant pain, a laparotomy was performed.

Under general anesthesia the abdomen was opened through a right-rectus incision. The uterus was enlarged to a size consistent with a 5 or 6 months' pregnancy. The right ovary was located, and beneath it was a dark mass roughly 4 by 3 cm. This mass was elevated and, by untwisting, was found to consist of the terminal two thirds of the right fallopian tube, which then resumed its normal position. The demarcation between the normal and hemorrhagic areas of the fallopian tube was definite, and the nonviable portion of the tube was removed with ease. To avoid premature termination of the pregnancy, manipulation of the uterus was kept at a minimum. The appendix, which appeared normal, was not removed.

The immediate postoperative course was marked by a gradual diminution of the pain. Discharge from the hospital was delayed by slow healing of the skin wound.

Since leaving the hospital the patient has been free of pain, and the pregnancy has progressed normally.

On pathological examination‡ the specimen consisted of a dark-brown mass of tissue 4 by 3 by 2 cm. On cut section there was a soft, red-brown and brown surface with one cystic space approximately 1 cm. in diameter. On microscopical examination the tube, lumen and wall were filled with red blood cells. The epithelium was largely destroyed, and that which remained was low columnar. It appeared that the congestion and hematosalpinx followed the torsion of the tube.

The rarity of torsion of the normal fallopian tube during pregnancy has been noted. McKerrow[1] reported such a case with involvement of the right tube, and Sheldon[2] discussed a case in which both the right tube and ovary had undergone complete torsion and become gangrenous. Two additional articles have appeared in recent years in foreign-language journals. Torsion of the tube after hematosalpinx is somewhat more common, and Savage,[3] in 1936, reported such a case and gathered 13 similar cases from the literature.

Because of the infrequent occurrence of this complication, the diagnosis is not made until operation. The majority of cases of torsion of the fallopian tube, normal or otherwise, during pregnancy have involved the right tube. In these cases the preoperative diagnosis of acute appendicitis was frequent and logical. In McKerrow's[1] case and that reported above there were findings suggestive of genitourinary disease, but in both cases cystoscopic examination was negative. Ovarian cyst with twisted pedicle, ectopic pregnancy in the fallopian tube and hydrosalpinx are other possible preoperative diagnoses.

SUMMARY

An additional case of torsion of the normal fallopian tube during pregnancy is reported. This rare complication is diagnosed correctly by laparotomy.

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MEDICAL PROGRESS

SYPHILIS* (Concluded)

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Serologic Response

A prolonged follow-up study of the pattern of serologic response after penicillin therapy for early syphilis is of utmost importance. A monthly quantitative test is desirable in all cases and should be performed for probably not less than a year. The quantitative determination of reagin titer at monthly intervals will enable the practicing physician correctly to assay the response to treatment and should warn him of an impending relapse before it becomes clinically manifest. In early syphilis adequate therapy with penicillin will usually reverse positive serologic tests to negative in about six months.[74] Some patients, especially in the late secondary or early latent stage, may require much longer than six months to become seronegative. Small amounts of reagin in the blood for longer than six months after treatment do not necessarily require retreatment. Conversely, a consistent slow rise in titer should indicate the need for repetition of a course of therapy. If the serum reagin titer does not show a steady and progressive drop during the first six months, another indication for retreatment is presented. These statements apply strictly to early syphilis.

Quantitative serologic examinations in the follow-up study of penicillin-treated syphilis not only are a guide in response to treatment and an aid in predicting an impending relapse but also may serve as a helpful means of differentiating serologic relapse and reinfection.[80] In relapses there is frequently a sudden sharp increase in serologic titer, after an apparent response to treatment that has not resulted in a completely negative test. Patients who become reinfected have usually attained and maintained complete serum negativity followed by the development of a new primary lesion at a new site with the development of seropositive reaction shortly thereafter. A new chancre should certainly be darkfield positive.

A comparison of the serologic response following penicillin therapy with that following previously established methods has been used to gauge therapeutic efficacy as shown by serologic cure.[81] Two hundred and eight patients with untreated primary or secondary syphilis were hospitalized and treated with three different schedules of penicillin therapy. The serologic response in these cases was compared with data from a similar series of patients who had been given arsenical treatment. The rate of fall of serum reagin was observed to be comparable in each group, although in some classifications the penicillin response was a little slower. If this is correct, it merely illustrates that the actual efficiency of penicillin is not remarkably greater than that of arsenic, when assayed from this one standpoint.

Combined Therapy

Numerous schemes combining penicillin with bismuth, arsenic, fever and so forth have been studied in a search for a possible ideal adjuvant to penicillin. So far there is no report of greater efficiency or anything like as low a rate of reactions as that seen with penicillin alone. One series of 1350 patients with early syphilis received a combination of mapharsen and penicillin.[82] After six months' follow-up study, 83.6 per cent were seronegative. The incidence of reactions was high. A small series of cases treated with bismuth and penicillin showed no better results than a control group receiving only penicillin.[83] One report is actually pessimistic about penicillin.[84] Another analysis compares groups of patients treated biweekly or triweekly with mapharsen or neoarsphenamine, massive arsenotherapy, penicillin alone and penicillin combined with arsenoxide and bismuth.[85] The most rapid response was obtained with arsenoxide twice weekly. The combined penicillin-chemotherapy group was seven weeks slower in serologic response, and the failure rate was approximately 17 per cent.

The combination of penicillin and fever therapy in early syphilis has been studied from the standpoint of increasing the favorable effects of penicillin in a given dosage and also the possibility of shortening penicillin therapy without the loss of efficiency.[86] The maximum dosage was 1,200,000 units of penicillin over a period of seven and a half days, in addition to three sessions of physically induced fever. The failure rate in this group was a little more than a third lower than that in a comparable group receiving the same amount of penicillin alone, but the result was distinctly less favorable than that after more satisfactory penicillin dosage without adjuvants. Attempts to shorten the penicillin-fever therapy to thirty hours were unsuccessful.

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These treatment schedules are technically more difficult to administer, and the likelihood of reactions is inescapably higher. The co-operation of patients would obviously be difficult to obtain in many cases.

Arsenotherapy

Reports of intensive treatment of early syphilis with triweekly injections of mapharsen and concomitant weekly injections of bismuth continue to appear.[87, 88] These are follow-up studies of rapid treatment schedules that were in the course of development just prior to the advent of penicillin. From nine to fifteen weeks were required to complete these schedules. The results were good, with as high as 90 per cent satisfactory cumulative percentage by the end of three years. Serious reactions were infrequent compared to more intensive massive-therapy schedules, but in comparison to penicillin the reaction rate and severity were high.

Relapse vs. Reinfection

The remarkably successful use of penicillin in the treatment of early syphilis has been clouded to some extent by the difficulty in ascertaining the true percentage of relapses as contrasted to reinfection. The relative ease of cure that is now available is bound to create a greater degree of carelessness among many less responsible citizens. The symptoms of an early infection can be relieved more quickly than the common cold in a large percentage of cases. With slight exaggeration, it might be said that a habitual offender could acquire new infections almost faster than each preceding one was cured. It is thus obvious that differentiating failure of treatment, or syphilitic relapse, and a true reinfection may present the most complicated of problems. For the benefit of absolute accuracy, the rates of failure with treatment as efficient as penicillin should therefore include all patients in a given series who require retreatment within at least the first few months following the initial course of therapy. Rigid criteria for the determination of relapse and reinfection, as practiced in the past, have of necessity been abandoned. Many such differentiations now appear to rest on clinical impressions rather than on certainty. One new set of criteria has been presented that seems to deserve consideration.[89] It is held that the diagnosis of syphilitic reinfection in persons previously treated for syphilis should require clinical evidence of a second infection preceding the serologic evidence. It is further stated that the response to a second treatment course should be similar both clinically and serologically to that seen with the previous infection. Epidemiologic evidence is held to be of distinct value. Exposure to a person with known infectious syphilitic lesions, followed by the development of the infection after a proper incubation period in the patient under consideration, is strong evidence of reinfection. Obviously the primary lesion should be a darkfield-positive chancre. The treatment of the preceding infectious episode must certainly have been adequate, or it would point to the likelihood of relapse. A period of seronegativity between the two infectious episodes is highly desirable in the effort to prove reinfection.

Late Syphilis

Less effort has been expended in the treatment of late syphilis with penicillin than any other stage of the disease. The results in late latent syphilis have been discouraging. In cardiovascular disease, the effects of penicillin are questionable. In other active phases of late syphilis, there is more encouragement, but it seems highly questionable whether penicillin alone should be depended upon.

In most forms of late active syphilis it is imperative to avoid Herxheimer reactions. This is particularly vital in visceral disease. Cole[90] has advocated that all patients with late syphilis receive a course of heavy metal (bismuth) in addition to potassium iodide preceding penicillin therapy to obviate the danger of reactions. This is excellent advice and might well be carried a step farther. A diagnosis of late latent syphilis may be correct as far as it is possible to determine, and yet the patient may have a concealed active lesion. Thus, it is equally appropriate to give a latent case the chemotherapy preceding penicillin.

There is fairly general agreement that late latent syphilis is a field in which penicillin treatment is far from proved in value.[76, 91-93] It is not yet known whether penicillin may be of preventive value in latent syphilis, although the efficacy of traditional chemotherapy has long been accepted in that respect. It will take many years to determine this point. Certainly, one should not rely on penicillin alone in either latent or active late syphilis until far more has been accomplished with this mode of treatment. The suggested dosage schedules in many cases are similar to those recommended for neurosyphilis.

In late cutaneous syphilis moderate doses of penicillin have been striking in their effect.[76] Not all late gummatous syphilis is responsive to penicillin.[94] Syphilis of the bone is known to respond satisfactorily to penicillin therapy in most cases.[76, 95] A word of caution should be interjected regarding these so-called benign forms of late syphilis. Their clinical response to any form of therapy may seem satisfactory, but serologic response is often exceedingly slow and sometimes apparently nonexistent. It must be constantly borne in mind that syphilis is a systemic disease and reliance cannot be placed upon the behavior of any one symptomatic phase of the disorder.

A survey of 550 patients with late syphilis treated by penicillin has appeared from the Johns Hopkins

Hospital and casts a decidedly questionable light on the value of this treatment.[91] Treatment failures are said to occur in the form of drug resistance, clinical progression, recurrence of lesions after an initially favorable response and the subsequent development of new manifestations of syphilis elsewhere in the body. A significant number of cases are presented, suggesting that penicillin may prove less efficacious in the later stages of syphilitic infection than during the more acute early phases of the disease. It is obvious that a great deal of further observation is required before penicillin may be considered lastingly efficacious in late syphilis. Perhaps this agent should be regarded as an adjuvant to traditional chemotherapy in some forms of late syphilis, rather than vice versa as considered in early stages of the disease.

Cardiovascular Syphilis

Several general reviews of the problem of cardiovascular syphilis and additional studies of special phases have been reported during the past year.

It is estimated that 10 per cent of all cases of early syphilis develop cardiovascular involvement.[92] This should be preventable by adequate therapy early in the disease. A survey of 177 cases of cardiovascular syphilis was undertaken to determine how many patients had received adequate treatment either during the early stages of their syphilis or during the latent period, and to determine the effect of treatment on advanced cases of syphilitic aortitis.[96] Exceedingly low percentages of all the types of cardiovascular syphilis were found to have had anything like adequate treatment in the early stages of the disease. Some of these patients were under observation for ten years or more. The authors were unable to determine definitely what effect, if any, specific antisyphilitic treatment had had upon prolonging the life of these patients. It was stated that treatment of uncomplicated syphilitic aortitis will often prevent the development of serious cardiovascular complications. Once aortic insufficiency or aneurysm has developed, it is questionable whether antisyphilitic treatment can arrest the process, and it must certainly be used with great caution. One reviewer states that syphilis of the aorta and its complications comprise 13 to 15 per cent of all cardiac diseases found at autopsy.[97] Another presentation discusses a study of 43 patients with syphilitic aortic insufficiency who had received standard chemotherapy and were followed from two to sixteen years.[98] The data indicated that there may be an asymptomatic phase of from two to ten years followed by a symptomatic period, which may last an additional two to fourteen years. Cardiac failure was found to be as readily controlled with digitalis and mercurial diuretics as in other types of heart disease. An analysis of 59 cases of aortic aneurysm is also available.[99] Only 25 per cent of these patients gave a history of a chancre. None were considered to have received adequate treatment. No difference was found in the appearance of the lesion in treated and untreated cases.

Therapy

All writers on this topic are in agreement that in the presence of cardiovascular syphilis, patients should be prepared with bismuth injections to prevent Herxheimer reactions.[71, 74, 97, 100] Individualization of the patient is imperative. Cardiac therapy should be the same as that for heart disease from other causes. Antisyphilitic therapy should be stopped if the patient is not improving or is growing worse, and treatment should be directed to the heart condition until cardiac signs and symptoms improve. Antisyphilitic therapy should invariably be withheld in the presence of cardiac failure. In the early days of penicillin there was considerable hesitance on the part of cardiologists to use this antibiotic in the treatment of cardiovascular syphilis. Experience has proved penicillin less dangerous to these patients than was at first believed. Initial doses as low as a few hundred units are advocated. One series comprised 28 patients with syphilitic aortic insufficiency and 8 with thoracic aortic aneurysm.[101] Total dosage varied from 2,000,000 to 15,000,000 units, and there was an absence of severe reactions throughout. Five patients had fever within the first sixteen hours of treatment, and 2 with long-standing angina at rest had attacks of usual severity and frequency during and subsequent to administration of penicillin. In no case was the treatment schedule interrupted. There was no significant difference in the incidence of reactions or cardiovascular symptoms in the patients who received small initial doses as compared with those who received 25,000 to 100,000 units for their first dose. The average total of penicillin therapy advocated has been 6,000,000 units in from ten to fifteen days.[71, 99]

One author states that there is too little knowledge regarding the treatment of cardiovascular syphilis with penicillin for this subject to be discussed intelligently.[97] He believes that the weight of evidence indicates that syphilitic aortitis will not be permanently arrested unless arsenical therapy is included in any course of thorough and prolonged treatment. The arsenical agent of choice is stated to be arsenoxide (mapharsen, chlorarsen or similar preparations). It remains to be seen whether this opinion is correct as further work with penicillin progresses. It may well be ten to twenty years before the question of penicillin therapy in complicated syphilitic aortitis can be settled.

Neurosyphilis

Next to early syphilis, more effort has been expended in the study of penicillin therapy of neurosyphilis than any other phase of the disease.

Results with penicillin have not been so dramatic as in early syphilis. The most outstanding effect has been favorable changes in the spinal fluid, particularly the cell count. There is considerable controversy regarding the question of using penicillin alone versus penicillin combined with fever therapy or other adjuvants in the treatment of neurosyphilis.

One of the most easily recognized objective findings in neurosyphilis and one upon which much reliance is placed is inequality of the pupils. The incidence of anisocoria was found to be nearly 17 per cent in a study of 500 normal subjects.[102] In 4 per cent of this group there was a pronounced difference in pupillary size. Inequality of the palpebral fissures was even more frequent. Imbalance of sympathetic innervation and differences in refractive errors are considered to be possible explanations for at least some cases of anisocoria. It is obvious that too much reliance cannot be placed upon this one objective finding in an attempt to establish a diagnosis of neurosyphilis.

In a study of 54 patients with syphilitic primary optic atrophy, it was found that loss of vision was the first manifestation of neurosyphilis in 63 per cent.[103] The optic atrophy was generally found to be accompanied by strongly positive cerebrospinal-fluid findings unless antisyphilitic treatment had been started. A majority of the cases exhibited the tabetic type of neurosyphilis. Fever therapy was found to be superior to chemotherapy in this series and the prognosis was not too unfavorable, provided that treatment was begun before useful vision had been lost. Of 16 patients given fever therapy in addition to chemotherapy, only 2 (13 per cent) were blind on follow-up examination two years or more after treatment. Another study led to the advocation of malarial therapy aided by concomitant and subsequent courses of penicillin, each course consisting of the administration of at least 5,000,000 units.[104] This work comprised a study of anatomic material of 12 cases of syphilitic primary optic atrophy, in 2 of which death had occurred at a time when the atrophy was confined to one eye. It was found that by the time demyelination of the nerve fibers had progressed to complete degeneration in one optic nerve, there was already present in the normal nerve a syphilitic inflammatory exudate that ultimately led to atrophy of the second nerve. It was stated that optochiasmatic arachnoiditis has nothing to do with the atrophy of the optic nerves.

In nerve deafness due to syphilis, penicillin has been found to be fully as effective as the older methods of therapy; only 13 patients with syphilitic deafness were studied, but this complication is not a common one.[105] Patients with acute syphilitic meningitis and deafness responded rather well. In late syphilis with deafness of longer duration, the response to penicillin therapy was less favorable and considerably delayed. Some patients showed no improvement, but there was no progression. One case of late congenital syphilis continued to show progressive loss of hearing. There was no evidence that penicillin has an unfavorable effect on hearing.

In severe, poorly regulated diabetes mellitus of long duration there may be neurologic changes that closely mimic tabes dorsalis (diabetic pseudotabes). Sensory disturbances, evidences of posterior-column damage, areflexia and a predilection for the lower extremities are common to both conditions. A group of 17 cases of neuropathic arthropathy of the feet associated with diabetes mellitus has been reported.[106] These patients had destruction of the tarsal or metatarsal bones that was roentgenologically similar to that observed in Charcot joints. It was pointed out that the Charcot joint is more likely to exhibit an acute onset of fluid with swelling of the extremity and is usually painful during the acute stage and that new bone formation can frequently be demonstrated in the Charcot joint, whereas these findings are seldom notable in the diabetic neuropathic foot. The Charcot joint is relatively less frequent in the foot than in other joints, whereas feet are the most common site of diabetic neuropathy. Two additional cases have been reported in which neurogenic arthropathy of the Charcot type in severe diabetes of long standing was accompanied by the development of cord bladder.[107] Here again are examples of the occurrence of lesions commonly designated as evidence of neurosyphilis in nonsyphilitic persons. Nevertheless, it is necessary to exert every effort to rule out neurosyphilis, regardless of negative serologic tests for syphilis, by careful clinical examination and lumbar puncture in patients such as those described. In other words, diabetic neuropathy should not be allowed to mask an actual case of neurosyphilis.

There is general agreement among syphilologists that spinal-fluid findings are of primary import in the diagnosis and management of neurosyphilis. It is not agreed, however, what constitutes normal standards for some of the tests done on the spinal fluid or what the different tests signify. There are four that should certainly be considered obligatory in all cases: cell count, total protein, colloidal gold and complement-fixation test. No single item will give complete information on the process involving the central-nervous system. An evaluation of spinal-fluid tests, based on thousands of examinations, has appeared from Bellevue Hospital.[108] The presence of 3 cells per cubic millimeter of spinal fluid is regarded as normal; 3 to 5 cells are considered to represent borderline values; and more than 5 cells are held to be definitely pathologic. The cell count should be a reliable indication of the activity of the process. The total protein determination in association with the cell count is a further indication of activity; normal values for total protein in the spinal fluid are stated to range from 10 to 30 mg.

per 100 cc. The colloidal gold test in its qualitative aspect gives a clue to the prevalent type of central-nervous-system tissue involvement, and its quantitative values offer an indication of the trend of the process. It is stated that in addition to a qualitative trend, a quantitative value may be obtained by addition of the ten figures of the colloidal gold test; a comparison of results is afforded with spinal fluids examined at various periods in the follow-up study of treated patients. The complement-fixation test should signify the specific nature of the syphilitic disease. Quantitative reagin readings, together with the other tests, provide additional information about whether the process in the central nervous system is progressing or abating or has been checked and thereby permit more intelligent management of a patient with neurosyphilis. Quantitatively determined spinal-fluid examinations have not been in general usage, but their value is being more widely recognized.[109]

Therapy with Penicillin Alone

Stokes and his associates[110] have presented a three-year study of penicillin alone in the treatment of neurosyphilis at the University of Pennsylvania; 361 patients were followed for periods of three months to three years. Of the total number of patients followed, spinal fluids were normal or nearly normal in over half; 74 per cent were markedly improved. Improvement in the spinal fluid appeared to level off in approximately 70 per cent of cases by the second year. Additional courses of penicillin produced little further improvement in most cases. In symptomatic neurosyphilis a single course of 9,600,000 units in aqueous solution given at two-hour intervals during a period of ten to fifteen days is under study. Asymptomatic neurosyphilis is being treated with penicillin in oil and wax. A comparison of the results of penicillin therapy and malaria suggested that penicillin alone is equal to or better than malaria in the management of neurosyphilis. In tabes dorsalis, the results with penicillin were considered to be twice as good after the second year as with malaria. Low initial doses (500 units) of penicillin, increasing to full dosage by the fifth day, were stressed to avoid therapeutic shock. A still greater percentage of satisfactory results is reported in the treatment of neurosyphilis with penicillin alone at Bellevue Hospital.[111-114] The total dose varied from 2,000,000 to 9,000,000 units, and the injections varied from 75 to 200. There were 301 patients with active neurosyphilis who were treated and followed from six to forty-five months, of which only 11 per cent had to be retreated. Of the original failures over half responded well to a second treatment with larger total doses of penicillin alone. The evaluation of therapy in this group of patients was based almost entirely on the results of repeated spinal-fluid examinations.

Another series of 141 patients received 4,000,000 units of penicillin, and the neurosyphilitic process was considered arrested in approximately 85 per cent of the cases.[115] Early neurosyphilis responded more satisfactorily, and in cases of this type the results were as good as those obtained from fever therapy. It was concluded that in late symptomatic neurosyphilis, fever therapy was the treatment of choice. A schedule of 6,000,000 units of aqueous penicillin in eighteen days is considered satisfactory by another author.[74] He believes that at least 90 per cent of neurosyphilis will be arrested by that amount of penicillin and states that 9,000,000 to 12,000,000 units of penicillin in oil and wax over a period of eighteen to twenty days will probably give comparable results.

To evaluate the effect of previous chemotherapy on the results of penicillin treatment of neurosyphilis, clinical and serologic observations were made in 45 patients followed for one or two years after subsequent penicillin treatment.[116] Total dosages of 8,000,000 to 12,000,000 units were given for eighteen to twenty-one days. Penicillin was considered superior or equal to malaria in the treatment of all phases of neurosyphilis with the possible exception of paresis. Mixed opinions regarding the use of penicillin alone versus penicillin and malaria in the treatment of neurosyphilis are expressed by other authors.[117-119] It is indicated in general that the more advanced and serious forms of neurosyphilis often require repeated courses of penicillin or penicillin and fever combinations to achieve success.

An analysis of the blood serologic tests in 213 cases of late symptomatic neurosyphilis treated with various amounts of penicillin and observed for periods of six to twenty-four months or more after treatment indicated that less than 10 per cent of the patients attained complete serologic reversal.[120] Increased penicillin dosage or repetition of the course did not increase the percentage of serologic reversal. These findings are in agreement with the generally observed fact that penicillin seems to have little effect in reversing the positive blood serologic tests to negative in late neurosyphilis.

Intrathecal administration of penicillin has been advocated from a few sources but has not received general approval. One series of 179 cases has been reported, but the results are not superior to those in most of the aforementioned penicillin schedules with intramuscular injection.[121] Reactions to intrathecal penicillin were stated to be about the same as those following routine lumbar puncture and less than those following Swift–Ellis treatments or malaria. Serious toxic effects have also been reported, however, and there is certainly little or no evidence that intrathecal administration is of greater therapeutic value in neurosyphilis than intramuscular injections.[119, 122]

Combination Therapy

A number of authors reporting studies of varied methods of therapy of neurosyphilis state that the combination of penicillin and fever therapy is the treatment of choice in neurosyphilis, especially in the later symptomatic varieties.[71, 76, 123] Assorted doses of from 4,000,000 to 20,000,000 units of penicillin are advocated in accordance with the type of neurosyphilis under consideration. Several methods of inducing fever have been employed, but malaria seems to be in more general use. There appears to be no striking difference in results whether the fever and penicillin are given concurrently or successively.

One study surveys progress as measured by the spinal-fluid examination among 458 cases of neurosyphilis treated with mechanical hyperthermy, malaria or penicillin in oil and wax with adjuvant chemotherapy.[124] All cases included in this group had a minimum observation period of six months. On the basis of failure rates, there were no significant differences among the three types of treatment in any diagnostic group. Penicillin appeared to eliminate activity in the spinal fluid more rapidly than the hyperthermy or malaria treatment. It should be remembered that this was not penicillin alone but with added chemotherapy. Various combinations of penicillin with fever or chemotherapy, or both, according to the type of neurosyphilis, are advocated elsewhere.[119]

A report from the Johns Hopkins Hospital on the treatment of 149 patients with neurosyphilis with penicillin alone or penicillin and malaria indicated that the patients in the latter group exhibited a more striking spinal-fluid response than those treated with penicillin alone.[125] The majority of patients had advanced neurosyphilis with pronounced spinal-fluid changes. Another series of 118 cases of neurosyphilis was managed in a similar fashion.[126] The combined penicillin and malaria therapy was generally administered to patients presenting the more serious clinical picture. The results for all types of central-nervous-system syphilis showed a distinctly superior clinical and spinal-fluid improvement after therapy in the patients given penicillin in combination with malaria as compared with those treated with penicillin alone.

The admittedly greater hazard of fever therapy, regardless of the method of induction, should largely discount its apparently somewhat greater value except in the more advanced and serious forms of neurosyphilis. Many patients in this category are so debilitated that fever therapy is out of the question and malaria therapy in particular has certain special contraindications. It is ardently hoped that improved methods of administration of penicillin will bring forth more evidence of its greater effectiveness in neurosyphilis.

Malaria therapy also presents a greater possibility of complications; studies in two series of neurosyphilitic patients gave laboratory evidence of impaired liver function in all or most of the patients.[127, 128] The degree of hepatomegaly could not be correlated with the severity of liver dysfunction. After termination of the malarial fever, most abnormalities gradually returned to normal. In no case was there evidence of permanent liver damage. Attention has again been called to the efficacy of thiobismol (sodium bismuth glycollate) in reducing the frequency of vivax malaria paroxysms without eliminating them completely.[129] This drug exerts an inhibitory effect upon half-grown parasites and thus facilitates temporary interruptions of malaria that may permit a full course of therapy without rapidly exhausting a patient who may be having daily febrile episodes. In quartan malaria, the use of thiobismol is less well understood, but it seems to be effective.

It is obvious that penicillin has a definite and established place in the treatment of neurosyphilis. Whether this antibiotic will prove sufficient by itself is yet to be determined. There is certainly evidence that in the more advanced forms of neurosyphilis, the combination of penicillin with fever and possibly with chemotherapy has a place. As stressed above, the preparation of patients with late syphilis with a series of bismuth treatments before any more dramatic form of therapy is given is an intelligent procedure. Neurosyphilis in its entirety falls within this category.

Syphilis in Pregnancy

The primary purpose of laws requiring a prenatal serologic test for syphilis is the protection of unborn children. Evaluation of these measures must therefore be in terms of the incidence of congenital syphilis. Many states have enacted such legislation, and a survey of the effectiveness of the law in 1 case was recently reported.[130] In a six-year period during the operation of this law, the population of the state showed a 34 per cent increase with a corresponding increase in the number of births, but the infant mortality for syphilis decreased from 0.50 to 0.15 per thousand live births. During the same interval the number of patients with congenital syphilis under one year of age reported to the state department of public health dropped from 163 to 74. This is a decrease in case rate from 1.60 to 0.54 per thousand live births. As reflected in these percentages, the effectiveness of the prenatal blood-test law is obvious.

The use of penicillin therapy for syphilis in pregnancy has been studied to a moderate extent, and the results appear most encouraging. A group of 287 cases of syphilis in pregnancy treated with penicillin has been reported from Bellevue Hospital.[131] Among the patients treated only during pregnancy, there was an incidence of 2.8 per cent

of congenital syphilis. This figure dropped to 1.2 per cent in a group of women who had been treated from one to twenty months prior to pregnancy. Even this low figure might have been avoided except for unobserved serologic relapse in 1 uncooperative patient. The recommended dosage is 4,000,000 units of penicillin in twelve days. Patients should be examined at monthly intervals throughout the remainder of the pregnancy with quantitative serologic tests for syphilis to determine evidence of possible relapse and the necessity for retreatment. It is stated that retreatment during subsequent pregnancies is considered unnecessary, provided the patient is carefully observed. In another series of 81 infants born of penicillin-treated mothers with early infectious syphilis, only 1 stillbirth due to syphilis was encountered, and all the remaining infants were normal.[132] This is a failure rate of 1.24 per cent. A comparable group of infants delivered of women who were treated by various methods of intensive arsenotherapy developed 10.7 per cent of congenital syphilis. That failure rate certainly indicates the superiority of penicillin therapy of the pregnant syphilitic woman. The authors present 2 case reports on mothers who produced infants free of syphilis despite the fact that they themselves showed mucocutaneous relapse after penicillin treatment.

A dose of 3,000,000 units of penicillin for syphilis in pregnancy is advocated from another source.[76] This amount of the drug was said to protect 95 per cent of the infants when given during the last part of the first trimester of pregnancy. It could be repeated in the third trimester if the mother's syphilis had not responded properly. Still another source recommends 4,000,000 units of aqueous solution of penicillin (every three hours, for 100 doses) with a protection rate of 95 per cent.[74] It is further stated that in all probability penicillin in beeswax and oil can be substituted for the aqueous solution, in the amount of 600,000 or 450,000 units daily for ten or fourteen days. These studies of the use of penicillin in syphilis of pregnancy tend to confirm earlier optimism.

One previous report of the use of massive arsenotherapy in early syphilis complicated by pregnancy exhibited a degree of success comparable to the best reported with penicillin.[133] The reactions to this treatment are excessive, and such hazards are unnecessary in the face of at least equally efficacious penicillin therapy without the dangers of chemotherapy. There seems little excuse for the continued use of arsenic in any pregnant woman with syphilis unless she is unable to tolerate penicillin in any form.

Congenital Syphilis

Except in early congenital syphilis, the treatment of this phase of the disease has always been productive of less satisfactory results than most varieties of acquired syphilis. Penicillin has so far brought about relatively little change in this situation. From the standpoint of the effect of penicillin on the serologic status of congenital syphilis, a series of 25 patients showed improvement in only 24 per cent of the cases.[93] Some authors have been most pessimistic about the effect of penicillin in congenital syphilis, one preferring the use of mapharsen and bismuth combined with fever therapy.[76]

Congenital neurosyphilis has been considered one of the most adamant varieties and has not infrequently been recalcitrant to all types of therapy. A group of 11 patients with congenital paresis has been studied for comparison of penicillin with penicillin and malaria.[117] Five received penicillin alone, and 6 were treated with the combined method. No significant difference was seen in clinical or spinal-fluid results.

Interstitial keratitis has always provided another complicated therapeutic problem. Klauder[134] reports a study of interstitial keratitis with particular reference to the results of penicillin therapy in a series of 72 patients. It was found that penicillin, like chemotherapy, does not prevent an initial attack of interstitial keratitis, involvement of the second eye, or recurrence of the disease in a previously affected eye. It was possible to evaluate results of treatment of 59 patients in terms of final visual acuity with refraction determined at intervals one to three years after therapy. The findings were compared with a similar group of 54 patients given adequate courses of fever and chemotherapy. There was no appreciable difference in the final visual acuity of the two groups. This lack of striking result in final visual acuity of penicillin-treated patients compared with older methods is consistent with clinical observations in which penicillin does not uniformly exert an immediately favorable effect on active interstitial keratitis. It has long been realized that antisyphilitic treatment is not ideal in the management of interstitial keratitis, but it does show results superior to those in untreated patients. Fever seems to be the most effective single form of therapy but should most certainly be supplemented by adjuvants. Penicillin should dispense with chemotherapy in this situation as in most other phases of syphilis. This opinion is supported by other observers.[117]

An efficient oral form of antisyphilitic therapy would be of great value for infected infants. There is a report of the use of penicillin dissolved in water and administered to normal uninfected infants at ages of one week to five months.[135] A dose of 25,000 units gave blood levels that were considered therapeutic for as long as three hours. Further pursuit of this work is surely warranted.

Treatment Reactions

Penicillin

One of the most remarkable benefits of penicillin has been its relative freedom from reactions, and yet no rose seems to be completely without thorns.

A small number of patients will develop erythematous or erythematopapular eruptions within the first day or two after the beginning of penicillin therapy. These are usually mild affairs, lasting but a few days, and do not require interruption of therapy. A slightly larger proportion of patients may have urticaria, which is more likely to occur about a week after the beginning of penicillin treatment but may appear as late as the tenth or twelfth day, and occasional cases of post-therapy urticarias have appeared from two to four weeks after completion of penicillin treatment. Infrequently, these will be severe with angioneurotic manifestations, erythema-nodosum-like eruptions, distressing arthralgias and fever. These more pronounced reactions may require a week or more to subside in spite of all therapy. In most of the urticarias the penicillin may be continued with the assistance of antihistaminic drugs. A still rarer complication is a vesicobullous or pemphigoid type of dermatitis, which can be violent and incapacitating. There is also occasionally observed a localized dermatitis at the site of injections of penicillin. These are ascribed by some to the subcutaneous deposition of the drug, but there is not general agreement on this point. These local reactions respond much better to the application of cold than to hot applications.

In a survey of the treatment of over 10,000 cases of syphilis with penicillin it was stated that no serious reactions were observed.[136] These authors likened the urticarial reactions to serum sickness. This phenomenon was observed in a few patients as long as two months after treatment had been completed. The incidence of erythematous and papular eruptions in this series was 0.25 per cent. Only 2 patients out of the 10,000 developed a bullous dermatitis, which was limited to the exposed surfaces of the upper extremities. Such a peculiar localization has not been generally characteristic of the bullous type of reaction and suggests the possibility of extraneous or secondary factors. Attention was called to the occurrence of exacerbations of secondary syphilitic lesions, which appeared from the sixth to the tenth day after the start of treatment. This gave the appearance of an actual relapse of secondary syphilis, but darkfield examination of serum from lesions was always negative. No additional treatment was given, and the lesions receded in four or five days. The patients in whom this occurred have had ultimate good therapeutic results from penicillin treatment. Such phenomena seemed to resemble a delayed Herxheimer reaction, although the authors state that the occurrence of a delayed Herxheimer reaction has not heretofore been observed.

It was pointed out in a study of cutaneous reactions to penicillin that patients whose skins are in an unstable equilibrium because of some exudative dermatosis may be poor risks with penicillin therapy regardless of whether it is topically applied or injected.[137] Such persons might easily be those who would be more likely to become sensitized to the antibiotic. The fact that severe allergic reactions can occur is stressed in another publication.[138] In a series of 5000 patients treated with penicillin in an Army hospital, there were 6 reactions of such severity that it became necessary to discontinue the drug. Four were urticarial, occurring early in the course of treatment; 2 were delayed and simulated serum sickness. Preadministration testing for penicillin sensitivity was found to be neither reliable nor practicable.

In a comparison of the incidence of significant penicillin reactions, data were taken from several schemes of therapy as employed on a nationwide basis in many thousand patients.[70] The rate of reactions per thousand patients was as follows: aqueous solution of penicillin 6.3; penicillin in oil and beeswax 3.1; aqueous solution of penicillin with arsenoxide 15.9; penicillin in oil and beeswax with arsenoxide 7.6. There were 16 deaths among a total of 162,278 patients: 15 in patients treated with aqueous penicillin with arsenoxide, and 1 in a patient treated with penicillin in oil and beeswax with arsenoxide. This is immediate confirmation of the hazard of combined therapy using arsenic as adjuvant therapy to penicillin.

BAL

Although less and less arsenotherapy is being employed, there is considerable literature regarding the value of the relatively new detoxifying agent for metallic therapy known as BAL (2,3-dimercaptopropanol). That BAL has a suppressive action on the treponemicidal effect of the trivalent arsenical preparations has been demonstrated.[139] Five patients with acute early syphilis were treated with BAL and oxophenarsine hydrochloride concomitantly. The organisms (*Treponema pallidum*) were found by darkfield much longer than they would have been under efficient arsenotherapy. After the termination of the experiment these patients were given sufficient penicillin therapy, and each experienced a Herxheimer reaction equal to or greater than the initial one seen after the first injection of arsenic, which prompted the author to assume that many viable spirochetes were still present at the time penicillin therapy was started.

Unusually good response has been reported with the use of BAL in a series of 44 patients with severe and widespread arsenical dermatitis and that of the acute exfoliative type.[140] Thirty-one of these cases were benefited by treatment, and healing was obtained in an average of twenty-one days. The earliest sign of response was subsidence of the edema. The successful treatment with BAL of severe thrombopenic purpura after antisyphilitic arsenotherapy has been accomplished.[141] There was complete recovery among 12 patients between the

ages of fifteen and thirty-nine years who had agranulocytosis incurred during arsenotherapy for syphilis and who were treated with BAL.[142] The most dramatic results with the use of this drug have been observed in the sharp reduction of mortality in arsenical encephalitis.[143] To be effective the drug must be administered within a few hours after the onset of this complication. The dosage of BAL is 2.5 to 4 mg. per kilogram of body weight. From four to six injections should be given daily for the first two days, with injections twice a day thereafter until recovery. BAL is considered a specific detoxifying agent for arsenic, mercury, gold and other heavy metals and is given intramuscularly. The antidotal action is considered due to its ability to remove the metal from combination with tissue proteins and the resultant excretion of a stable and relatively nontoxic substance. A review of the subject of postarsenical encephalopathy has recently appeared.[144] Two cases encountered before the days of BAL were described therein, with a description of post-mortem observations. This complication should fortunately be exceedingly rare hereafter with the steadily decreasing use of arsenotherapy.

The successful treatment of tryparsamide optic neuritis with BAL has been reported.[145] The usefulness of BAL in poisoning from metals other than arsenic is known. There is recorded another case of successful BAL therapy in gold intoxication.[146]

The use of BAL is not unattended by reactions. Patients frequently complain of a tightness in the throat and an oppressive feeling in the retrosternal region. There may be burning of the lips, lacrimation, dryness of the mouth, nervousness and restlessness for periods of several minutes to an hour after treatment. Some patients experience considerable nausea and vomiting. Localized soreness and occasional abscess formation may be observed at the site of injection. The latter is particularly notable in patients with exfoliative dermatitis, as might be expected. Although no severe toxic reactions have thus far been reported, there is experimental evidence of enhanced toxicity of BAL in the presence of hepatic damage.[147] When BAL was injected into animals with severe renal impairment, no evidence of more toxic effects than those in normal animals was obtained.

Other experimental work indicates that thiamine in conjunction with BAL should exert a decidedly complementary effect in the treatment of arsenical toxicity.[148] A severe disturbance in carbohydrate metabolism during intensive arsenical therapy was noted during this experimentation.

Summary

Despite a slight increase in infectious syphilis among the civilian population in the past year, the combined total of early disease among civilians and military personnel has shown a slight downward trend. A ten-year survey of the deaths from syphilis revealed a most encouraging decrease. Control measures are being intensified throughout the country, with emphasis on public education, follow-up study of contacts and recognition of the role to be played by practicing physicians.

Improvement in the repository types of penicillin and wider employment of these products have facilitated the ambulatory treatment of syphilis and greatly reduced its cost to both patients and hospitals. It is surely the most practical approach and maintains adequate therapeutic levels with but one injection in twenty-four hours. For early syphilis, ten daily injections to total 6,000,000 units is the average recommendation, but more may often be advisable. There is continuous investigation of retardants to delay absorption and excretion of penicillin. Adjuvant therapy of assorted types is receiving further attention.

Penicillin G appears to cure about 90 per cent of early cases of syphilis among human beings, but it must be remembered that these patients have been so far followed for but a few years at most. The optimal therapy schedules have not yet been agreed upon, nor is there unanimity about methods of administration. The time-dose relation must be further clarified. Nevertheless, penicillin therapy of syphilis is obviously established by virtue of its shorter time requirement, relative simplicity and strikingly low rate of complications.

Neurosyphilis can apparently be arrested by penicillin in decidedly less time than by any other form of treatment, but adjuvant therapy may have a place in advanced cases. Other types of late or latent syphilis appear to be less favorably affected. All late cases of syphilis, symptomatic or latent, should receive bismuth therapy prior to penicillin to help guard against a therapeutic paradox.

Infection of the fetus will almost invariably be prevented or cured by adequate penicillin treatment of syphilis during pregnancy. Congenital infection is less responsive.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

EDITH E. PARRIS, *Assistant Editor*

CASE 35111

PRESENTATION OF CASE

A one-year-old male child was referred to the hospital from a well-baby clinic, where an abdominal mass had been discovered.

The patient was the younger of two living children, and no irregularities were detected regarding his birth, feeding or development. Within the two months preceding admission the mother had noticed a firm and painless mass in the child's left flank. He had had constipation, usually relieved by prunes and bran, most of his life, but the mother denied noticing any hematuria.

FIGURE 1.

Physical examination revealed a well developed and well nourished, alert child in no apparent distress. No lymph nodes were palpable. A prominence of the entire left abdomen was obvious by inspection, and many veins were visible over the abdomen. These were not engorged or tortuous. On palpation the mass was described as being firm, smooth and extending from beneath the left costal margin to the pelvic floor. A small notch was palpable on its medial surface at the level of the umbilicus; the lateral edge was not definitely palpable. There was no evident descent of this mass on inspiration. The liver and right kidney were not palpable. Examination of the chest was essentially negative.

The temperature was 100.2°F., the pulse 110, and the respirations 20-26. The blood pressure was 90 systolic, 50 diastolic.

Laboratory examination revealed a white-cell count of 9300, with 30 per cent neutrophils, 64 per cent lymphocytes, 4 per cent monocytes and 1 per cent eosinophils. The hemoglobin was 9.9 gm. The red blood cells showed some hypochromia and anisocytosis. The platelets appeared normal. The urine had a pH of 5.0, with a specific gravity of 1.022. The sediment showed 1 or 2 white blood cells per high-power field and amorphous crystals. The nonprotein nitrogen was 30 mg. per 100 cc. Nose and throat cultures revealed a few alpha-hemolytic streptococci and *Staphylococcus albus*. A tuberculin test was negative in a dilution of 1:1000. X-ray examinations of the chest, skull and thoracolumbar spine showed no evidence of intrinsic disease. A plain film of the abdomen disclosed a large, oval tumor mass on the left, extending partially across the midline. This could not be separated from the shadow of the left kidney (Fig. 1). There was no visible evidence of bone erosion or calcification within the mass. Intravenous dye was excreted slowly on the left, showing marked dilatation and upward displacement of the calyxes and pelvis. Excretion on the right appeared within normal limits (Fig. 2).

Operation was delayed because of an upper respiratory infection. However, on the tenth hospital day, following transfusion and preoperative doses of penicillin and streptomycin, an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. THOMAS H. LANMAN*: A painless mass in the left upper abdomen in a one-year-old child brings to mind right off some form of malignant lesion. But before considering cancer in detail we might go through the history, which has some significant points.

The prominence of the abdomen fits in with the tentative diagnosis I have in mind, and the appearance of the veins is interesting but not diagnostic.

The mass is described as firm. I judge it extended into the renal fossa but not into the pelvis. The

*Surgeon, Children's Hospital, Boston.

notch makes one consider the spleen, but as we shall see later it was probably not the spleen. The mass did not descend on inspiration, indicating that it was fairly well fixed. The right kidney was not palpable. The white-cell count showed only a relatively high percentage of lymphocytes, and I do not believe this is significant. There was slight anemia but nothing else abnormal in the blood examination, which is of some significance in excluding certain possibilities such as splenic enlargement.

The finding of streptococci in the nose and throat cultures was probably incidental.

The negative tuberculin test may be significant in some cases but does not enter into this differential diagnosis.

In summary, we have a firm mass that had pushed the intestines over toward the midline. The intravenous pyelogram shows distortion of the kidney pelvis and calyxes. Here is a homogeneous mass pushing the bowel over to the opposite side, filling almost the entire abdomen on that side, and possibly extending to the midline but not beyond it. A solid tumor, especially in this age group, should be regarded as malignant until proved otherwise. I do not see anything in the history or in the blood examination to suggest disease of the spleen. The only thing here that might make one think of the spleen is the mention of a notch in the mass. There is nothing to suggest an enlarged spleen caused by either purpura or Banti's syndrome, nor is there anything to suggest hemolytic icterus. One would not expect a spleen of this size at this age without other symptoms of splenic disorder.

What other masses may there be? There are certain benign cysts, and the duplications of the intestinal tract. Cysts of the mesentery are, as a rule, not at all firm. They may attain a size as great as this but would be almost sure, even at this age, to give some gastrointestinal symptoms such as subacute obstruction, vomiting or loss of weight.

A duplication is usually cystic on palpation, but it may feel solid as this did, although it is extraordinarily rare for it to be both large and solid. If attached to the stomach or the bowel and of this size, I believe it certainly would have given something in the way of pressure symptoms and gastrointestinal symptoms.

With a hydronephrosis an enormous mass can occur, but the intravenous pyelogram would not show the abnormality of the pelvis, which we see here. This film shows displacement and compression of the calyxes rather than dilatation from a congenital obstructive lesion causing a hydronephrosis in that kidney.

We come now to the types of malignant tumor usual in this age group and in this region. There are two: the embryoma, or Wilms tumor, and the neuroblastoma. In differentiating these two one can sometimes make a good preoperative guess, although not always. Such a case is a good illustration of when the treatment is surgical, and the mass should be explored.

In addition to the Wilms tumor and neuroblastoma there are rare conditions that one must consider. The true hypernephroma, or Grawitz tumor, we have never encountered in this age. In addition to the Wilms tumor it is possible to have an embryoma arising retroperitoneally from the remains of the primitive mesonephron, which is

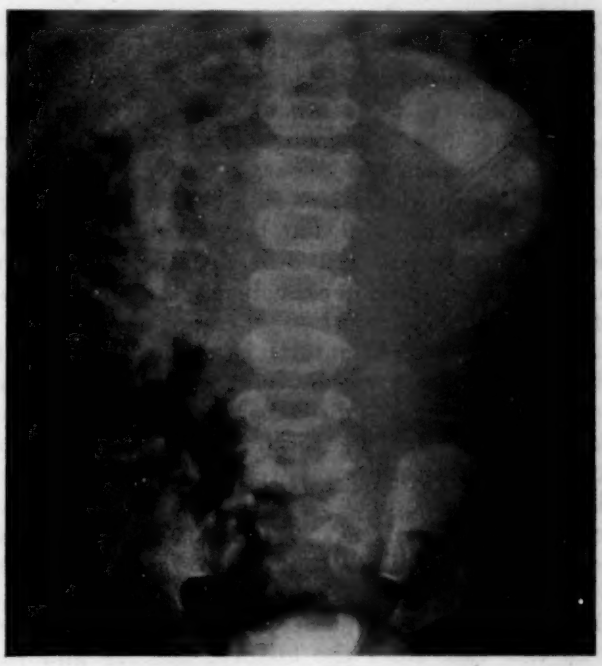

FIGURE 2.

not attached to the kidney. These are hard to differentiate, but if one attained this size, this picture in the pyelogram, which suggests that the growth is in the kidney itself, would hardly be expected. In considering neuroblastoma, which is by far the commonest of the tumors of neurogenic origin, there are other tumors from the sympathetic system that one might perhaps encounter. Certainly the ganglioneuroma can be quite large, but such size is unusual as early as this.

Adrenal cortical tumors certainly would not attain this size without symptoms; characteristically they are small and, of course, give as outstanding symptoms changes in sex: in the male, sex precocity, and in the female, a tendency to masculinization.

The Wilms tumor and neuroblastoma are about even in incidence in our series — 93 of the former and 100 or more of the latter. There is not enough difference in numbers to be significant in differential diagnosis. A Wilms tumor usually occurs in early life — most of our cases between two and three

years of age, although we have seen the tumor in patients as young as two months. The neuroblastoma is likely to occur a little later. Three quarters of our cases of neuroblastoma have occurred at four or five years, although we have seen neuroblastoma as early as the seventh day of life. The physical examination perhaps gives a better differential than anything else — that is, the size, the shape and the feel of the mass. The Wilms tumor is smooth or somewhat lobulated, and I would imagine that the notch here was a lobule such as occurs in this type of tumor. A neuroblastoma is more likely to be nodular and rough. It is not always possible to differentiate. It is suggestive that the neuroblastoma usually does not attain such a size as soon as this. Very frequently in cases of neuroblastoma the attention of the mother or the physician may be focused upon the metastasis — that is, there may be evidence of metastasis before the tumor itself is found. Metastases may be seen in the lungs and bones of the skull, but they frequently appear in the long bones. In differentiating these two tumors it is sometimes valuable to take films of the long bones.

The absence of hematuria is not at all unusual. Hematuria is a rare symptom of a Wilms tumor, and certainly not more than a quarter of the patients have had hematuria as a presenting symptom. It is interesting to observe that in such cases the growth had broken through its capsule into the renal pelvis, and as a prognostic sign gross hematuria in a Wilms tumor is a very grave one: we have no case of cure when gross hematuria has been present preoperatively.

In this case from the history, the age and the described feeling of the mass and from the x-ray appearance, I shall make the diagnosis of a Wilms tumor.

Dr. Tracy B. Mallory: Dr. Wyman, would you like to comment on the films?

Dr. Stanley M. Wyman: I think there are perhaps one or two points to mention. The portions of the mass that one can see extending upward and laterally are extremely smooth in contour. The mass is homogeneous and shows no unusual calcification. The lateral view demonstrates the mass extending downward and extremely far anteriorly up to the abdominal wall. It does not appear to lie very far posteriorly. That is suggestive evidence, not conclusive, but the mass may lie more anteriorly than the kidney. Unfortunately, we do not have pyelogram films taken in an oblique position to determine this. There is a hint of a capsule on this mass, but it is not very definite, and I am not sure it is a valid finding. However, the whole picture raises an additional question in my mind: could this be a cystic lesion, possibly bowel duplication or mesenteric cyst, although it certainly does not sound that way from the physical examination? The large bowel seems to be displaced medial rather than lateral to it.

Dr. Lanman: If that is a suggestion of capsule, it would fit in more with a Wilms tumor than with a neuroblastoma.

Dr. Gertrud C. Reyersbach: We wondered clinically about one thing. Was it not a very long interval? It was two months since the mother had discovered the mass, and was not the child apparently well?

Dr. Lanman: I do not think that is particularly against a Wilms tumor. These growths go along quite locally and may go for some time. That is one of the most characteristic symptoms we have in our series — that the mother was the first to notice the tumor. The two-month interval here would not be against that diagnosis, though usually the mother seeks advice sooner.

Dr. J. Gordon Scannell: I think that there was universal agreement on the service with the differential diagnosis as given by Dr. Lanman. We believed that we were dealing with a malignant tumor and that probably its vascular supply came from above and medially. We therefore elected to explore transthoracically and obtained excellent exposure of the vessels without disturbing the tumor itself. The renal vein was not very large and was divided first. Next the renal artery, as well as a few soft nodes which lay adjacent to it, was secured close to its source. The adrenal gland had previously been clearly visualized, was quite normal and was preserved. The tumor itself was a rather firm, oval mass without great vascularity. It obviously arose in the lower pole of the left kidney. With the vessels previously ligated, the kidney and its tumor were readily delivered and removed. About 15 or 20 cm. of ureter was removed with it.

Dr. Benjamin Castleman: Would you have given x-ray treatment preoperatively?

Dr. Lanman: No.

Clinical Diagnosis

Wilms tumor.

Dr. Lanman's Diagnosis

Wilms tumor.

Anatomical Diagnosis

Cystic teratoma of kidney, benign.

Pathological Discussion

Dr. Mallory: The tumor was a considerable surprise to all of us since it turned out to be cystic and looked, in fact, almost exactly similar to a multilocular ovarian cyst (Fig. 3). One can see in the lantern slides that the lower two thirds of the kidney have been replaced by a multilocular cystic structure. Some of the cysts have thin and transparent walls; others are opaque. There were a few masses of solid tumor, and those that we found appeared to be fibrotic.

In microscopical sections from this tumor the cysts are lined by a very low, nonspecific-looking, cuboidal epithelium or possibly endothelium. The interstitial tissue consists almost entirely of fibrous tissue, most of which is well differentiated, although some is cellular in places and here and there, scattered through the tumor, are multiple, well differentiated, striated muscle fibers. These convince me that this was a teratoma that had differentiated in only two or three directions. We found nothing suggestive of teeth, hair, squamous epithelium and so forth, such as we sometimes find in teratomas. Teratoid tumors, of course, are found in the kidney and in the region of the kidney. Sometimes it is difficult to decide where they actually

FIGURE 3.

arise. In this case there is no question that the tumor was intrarenal and was occupying the entire lower pole. I have never seen a tumor of this character, although I do not know whether in the material at the Children's Hospital you have.

DR. LANMAN: No, we have not. What do you think about its degree of malignancy?

DR. MALLORY: I think it was probably benign. We could find no foci typical enough to suggest malignancy. I would offer a good prognosis in this case.

DR. LANMAN: I think it is an interesting case, and it is certainly new to me as a type of tumor in this region. The history is characteristic of embryoma. I think the treatment is the same in any case, and it brings out that exploration is the only way to decide what the tumors are. We are very much against the punch-biopsy type of diagnosis and are against preoperative radiation. I recently looked up our series of 93 cases of Wilms tumor from 1914-1947 and was encouraged to find that we have an over-all cure rate of 35 per cent. From 1914-1930 there were 26 cases with 4 cures, a 15 per cent survival; from 1931-1939, 30 cases with 10 cures, a 33 per cent survival rate; from 1940-1947, 37 cases with 19 cures, a survival rate of 49 per cent. We regard a two-year postoperative interval with no symptoms of recurrence as a cure in this condition. But the most interesting feature in this study is that of these 93 cases, 63 per cent of the cures have been in patients one year old or younger, and in the last studied group, 1940-1947, 80 per cent of the cured patients among the 37 cases were younger than one year. In other words, it is in the early age group that prognosis appears to be best. Here is a condition that certainly justifies routine examination in the early months or years of life because these tumors frequently give no symptoms whatever until the mass is noted by the mother or by a physician. This present case is an extremely interesting type of tumor. I have never seen one like it.

CASE 35112

PRESENTATION OF CASE

First admission. A twenty-six-year-old woman was admitted to the hospital because of hemoptysis.

Six years before admission the patient was suddenly seized with pain in the left lower chest. This was accompanied by fever and malaise. The fever and pain disappeared in the course of ten days. Two weeks later she developed a dry, hacking cough, which soon became productive. She did not return to work as a playground instructress for three months and shortly after this began coughing blood, about 7 cc. daily, for four or five days. She had lost 20 pounds since the onset of the illness. The next three years were spent in bed, during which time a diagnosis of bronchiectasis of the left lower lobe was made. Treatment by weekly bronchoscopies and postural drainage cleared all the symptoms. She was perfectly well until six months before admission, when she had a repetition of the first illness. In spite of postural drainage and therapeutic bronchoscopies the bleeding continued.

Physical examination revealed dullness and flatness over the left base, decreased breath sounds and a few, fine rales. A chest x-ray was reported as follows:

> There is a rounded, sharply defined, dense shadow lying in the costovertebral angle on the left side just above the diaphragm. This shadow measures about 2 cm. in diameter and has very smooth, sharp borders. There is also generalized haziness in the lung field medial to the shadow. This shadow has the appearance of a foreign body. After injection of lipiodol there are numerous, dilated, clubbed bronchi in the lower lobe. The shadow previously described has the same density as lipiodol, probably representing a puddle of lipiodol from a previous injection.

A left phrenicectomy and left lower lobectomy were done. Except for phlebitis the convalescence was uneventful. On x-ray examination two months

later the stump of the main bronchus of the lower lobe appeared slightly widened and had some minor bronchi branching off in this region. These bronchi were surrounded by a soft-tissue mass, measuring about 5 cm. in diameter, which may have represented the residue of the lower lobe.

Second admission (fourteen years later). Following discharge the symptoms all cleared except for hemoptysis, which occurred at intervals of six to twelve months. The episodes were not associated with coughing. Six months before admission the patient noted increased frequency of hemoptysis and a sense of tightness beneath the lower sternum. This was associated with the taking on of extra household responsibilities. Usually the amount of blood varied between 30 and 90 cc. The episodes occurred mostly at night and every two or three weeks. There were no other symptoms.

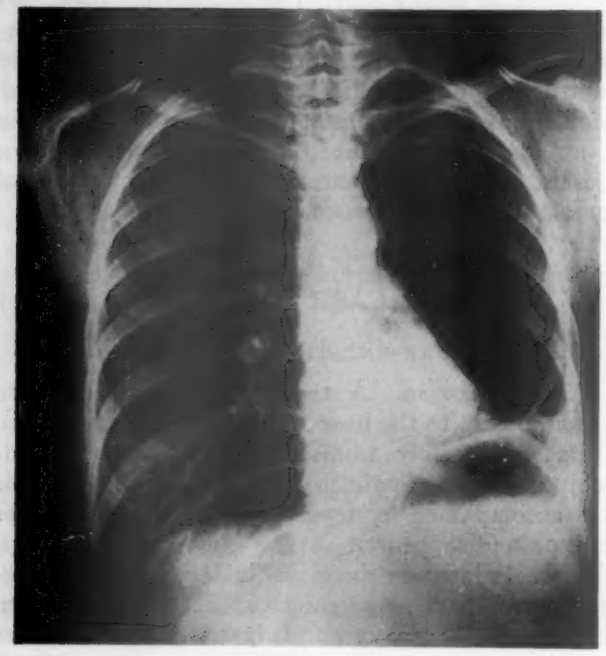

FIGURE 1.

The temperature was 99.2°F., and the pulse, respirations and blood pressure were normal.

There were dullness, decreased tactile fremitus, decreased bronchovesicular breath sounds and decreased spoken and whispered voice over the left posterior lung base. The hemoglobin was 12 gm.; the white-cell count was 7900, with a normal differential. The urine was normal. An x-ray of the chest was reported as showing a rounded area of increased density, 5.5 cm. in diameter, in the posterior portion of the left chest at the site of the previously resected left lower lobe. The upper margin of this soft-tissue shadow was adjacent to the intermediary bronchus on the left. The left leaf of the diaphragm was elevated. There was thick pleura in the left base; this was probably the result of the previous operation. The left upper lobe and the right lung were clear. There was a slight shift of the mediastinum to the left (Fig. 1 and 2).

On the second hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. JOHN W. STRIEDER*: Whatever the cause of bleeding, which began some twenty years before entry, it was obviously not relieved by the left lower lobectomy, which was performed fourteen years before entry. It may therefore be assumed that the cause was not in that portion of the lobe removed at the time of lobectomy. I say "portion" advisedly because in that era tourniquet lobectomy was the universal technic whereby pulmonary tissue was removed. For those who are not derived of that era, let me say that tourniquet lobectomy removed varying amounts of the lobe and left stumps of varying size, containing varying lengths of residual bronchi depending upon the site of amputation of the lobe. The pedicle was treated with hemostatic ligatures of catgut and, usually, pleuralized. In treating patients by modern operative technics a number of years after lower lobectomies by the tourniquet method, I have been impressed by the amount of pulmonary tissue that had been left.

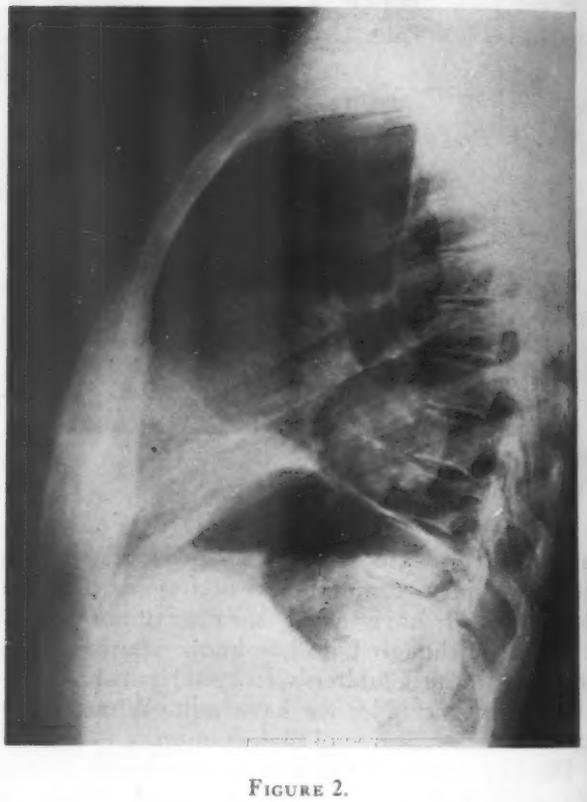

FIGURE 2.

*Surgeon-in-chief for thoracic surgery, Boston City Hospital.

It has frequently been a source of wonder to me that the operation was so often successful to the degree that it was.

At this point the exercise, therefore, resolves itself into a discussion on the basis of deduction to determine the source of bleeding. Was it in the left lower lobe, or was it in some other portion of the bronchopulmonary system? I think it is reasonable to assume on the basis of the record, there being no evidence to the contrary, that this patient's bleeding did come from the left lower lobe. So that it remains to determine what the nature of this lesion was that persisted in troubling this woman by repeated hemoptyses over a period of twenty years.

May we see the x-ray films?

Dr. Stanley M. Wyman: These films of the chest show the left leaf of the diaphragm to be elevated, with thickening of the superior border as a result of the old operation. The heart and mediastinum are displaced slightly toward the left. The overexposed grid film demonstrates a somewhat lobulated, homogeneous, sharply defined shadow in this region, which lies just about at the end of the stump of the left-lower-lobe bronchus. The shadow is seen in the lateral view to lie posteriorly, also in apposition with this major bronchus.

Dr. Strieder: Would you have any opinion about its density? Is it a solid tumor? Is it consistent with a cyst filled with fluid?

Dr. Wyman: Unless the cyst contains fairly fatty material, I believe it would be the same density as a soft-tissue tumor. The suggestion of perhaps a little lobulation makes one wonder about the actual soft-tissue mass. There is a little irregularity of the contour. This is insufficient to allow me to say whether this is definitely a soft-tissue mass or a cyst, although I would lean toward the former.

Dr. Strieder: Are there flecks of calcium in it, or are these densities due to overlay?

Dr. Wyman: I think it is overlying the shadow. The lung fields otherwise appear clear.

Dr. Strieder: So we have evidence of a round density, which, by comparison with the description of the films taken fourteen years previously, two months after operation, is similar in size, contour and density. The original films are not available, of course. The nature of the shadow described in the original films as being possibly a foreign body and then described as of the same density as the lipiodol (and therefore suspected of being a residuum of a previous lipiodol injection) is a matter of conjecture. I think one cannot say more than that about it. That shadow was not present after the operation, so that whatever it was, it was apparently removed at the time of lobectomy.

Given an x-ray shadow that is suggestive of tumor within the thorax, any discussion as to the exact histopathology of the tumor resolves itself into a more or less philosophical exercise that, at best, is a poor substitute for the microscope once the specimen has been handed to the pathologist by the surgeon. The cogent question at the present is, What lesion that is familiar to me best satisfies the many facets of this history and would give all the end results described? To me, by all odds, the so-called bronchial adenoma best satisfies this history. Going back over the history, the onset suggests bronchial obstruction followed by atelectasis, with infection and the subsequent development of bronchiectasis. The patient had intermittent bleeding for twenty years in varying amounts. These occurred during the third and fourth decades in a woman who, at the onset, was nineteen or twenty and who, at the time of the last admission, was about forty. This also is consistent with so-called bronchial adenoma. She had a long course of bronchoscopies, and certainly during the course of these bronchoscopies it might well have been suggested that she had an obstructive lesion in the nature of an adenoma causing her difficulty. However, we have no information on that, and of course it is entirely possible that the tumor was beyond the range of vision of the bronchoscopist. But full cognizance was not taken of the obstruction or the compression that it might have caused. She came to operation, and a tourniquet lobectomy was performed. A small tumor, suitably located extrabronchially in relation to the intermediary bronchus, could have escaped inclusion in the amputated specimen. That is a possibility that we have to consider. We do not know what the specimen showed at the time of the original removal. If the lesion escaped, as I think we can assume it did, that is a satisfactory reason for her continuing to spit blood up to the time of her last admission. If it was an adenoma, the question comes up whether or not it had undergone malignant degeneration as these tumors are alleged to do by many competent observers. We have no

evidence from which I can deduce that it had undergone malignant degeneration, but I would say that the periodic hemoptoic episodes were against cancer. The malignant tumor that ulcerates tends to bleed day after day for periods in small amounts rather than to cause small, frank hemoptyses, which are consistent with adenoma.

Of course, other causes of bleeding should be considered. Tuberculosis is not suggested in any way by the films, the course or the laboratory data with which we are furnished. Other tumors that cause bleeding most commonly are the malignant tumors. Benign tumors, other than the so-called benign adenoma, are likely to cause bleeding on the basis of obstruction and infection. Again, we have no way of knowing whether she had obstruction with bronchiectasis and bleeding from it alone.

One other hypothetical possibility that appeals to me — it is hypothetical because I have not encountered it personally, nor have I seen it described in exactly this situation — is that the original episode was on the basis of infection and atelectasis and that she developed bronchiectasis without an obstructing lesion in the bronchus. In that case, she bled on the basis of bronchiectasis, and when the lobe was amputated by tourniquet lobectomy radicles were left from which she continued to bleed. To go farther, she may well have developed a bronchiectatic cyst by the same mechanism that we have seen bronchiectatic cysts develop in residual lobes unrecognized as having disease in them prior to the time of operation. Against this is the fact that she is not described as having sputum. We would expect her to have sputum unless there was complete isolation of the cyst from the main bronchial tree. There were no febrile episodes. I would think somewhere along the line she would have had a bout or two of fever, if a reservoir had developed. Finally, as described by the radiologist, the tumor appears solid rather than cystic, but this of course is relative. So although this possibility is attractive, I would discard it in favor of my first impression, and say that this patient had bronchial adenoma with the question of malignant degeneration.

Clinical Diagnosis

Bronchial adenoma.

Dr. Strieder's Diagnosis

Bronchial adenoma.

Anatomical Diagnosis

Bronchial adenoma.

Pathological Discussion

Dr. Tracy B. Mallory: At this point the aid of the bronchoscopist was sought. Will you tell us your findings, Dr. Benedict?

Dr. Edward B. Benedict: Bronchoscopy showed a small, round tumor about 1 cm. in diameter below the left-upper-lobe orifice, which bled rather easily. It was far enough below the orifice that I thought simple resection of the stump of the bronchus could be performed.

Figure 3.

Dr. J. Gordon Scannell: This patient was operated on by Dr. Edward D. Churchill on both occasions — in 1935 and again recently. As Dr. Strieder pointed out, a tourniquet lobectomy was done fourteen years previously. It is well recognized that a surprising amount of lower lobe may be left behind on such occasions. Apparently, there was no evidence at that time of an adenoma, and the procedure went uneventfully. At the second operation a tumor was obvious, lying in the region of the resected lobe, and this remnant was 4 or 5 cm.

in its three dimensions. It lay under the upper lobe, very much like a ball in a catcher's glove, and although endoscopically it might have been resected without sacrificing the upper lobe, surgically the blood vessels, arteries and veins to the upper lobe made it impossible to resect and preserve that lobe, and a pneumonectomy was therefore completed. That was done for technical reasons and not with the idea that this was a malignant tumor. There were no suspicious lymph nodes seen at operation.

Dr. Mallory: I have a picture of the resected specimen (Fig. 3). This is the upper lobe. I do not think that one can quite see the intrabronchial tumor. It was comparatively small, about 0.5 cm. in diameter. External to that was this quite large mass, varying from 3 to 4 cm. in diameter, lobular, quite firm and apparently well encapsulated. There were a number of regional lymph nodes, none of which appeared to show any involvement. Histologically this was a very characteristic bronchial adenoma of the type that closely resembles the carcinoids of the intestinal tract. The tumor consists of small bundles of epithelial cells anastomosing very widely with one another. The cells are uniform in size and character and occasionally in places in the tumor there is a suggestion of gland formation, but these are not true glands. They represent areas where the stroma has degenerated, leaving an apparently cyst-like space. These tumors are not infrequently invasive and do occasionally show metastases to regional lymph nodes and rarely show distant metastases. In this case, in spite of twenty years' duration, it had not reached the lymph nodes.

Dr. Alfred Kranes: Did the original specimen show anything more than bronchiectasis?

Dr. Mallory: That is all. The amputation had been below the level of the main bronchus. These tumors are often dumb-bell in shape, with a small nodule within the lumen of the bronchus and another nodule outside the wall. The external tumor is sometimes very much larger than the internal tumor, as it was in this case.

Dr. Strieder: I have not heard you state recently your impressions of the possibility of malignant degeneration of these tumors.

Dr. Mallory: I have not seen any histologic evidence of a shift of the degree of malignancy. I think they are potentially of very low malignancy, and the ones that do invade and reach the regional lymph nodes do not look under the microscope any more malignant than the others. I think the situation is exactly analogous to the carcinoids of the intestinal tract, which can also be locally malignant and rarely produce distant metastases.

Dr. Strieder: You believe, then, that bronchiogenic carcinoma is never on the basis of such a precursor?

Dr. Mallory: I do not believe there is any connection between them.

Dr. Benjamin Castleman: I believe we have had 40 or 50 cases of adenoma of the bronchus, and in only 1 was there a metastasis to a regional lymph node.

The New England Journal of Medicine

Formerly
The Boston Medical and Surgical Journal
Established 1828

Official Organ of
THE MASSACHUSETTS MEDICAL SOCIETY
and
THE NEW HAMPSHIRE MEDICAL SOCIETY

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MEDICAL MANPOWER

IN THESE feverish days of reports, programs and proposals, a report has just appeared that is of vital interest to every thoughtful citizen and particularly to the physician, because its central theme is medical manpower. It is the so-called Voorhees report, the unanimous report to the Hoover Commission of the 11 medical and 5 lay members of the Committee on Federal Medical Services. This eighty-nine page document, supported by twelve detailed appendixes, is factual, unbiased and affirmative. It describes the magnitude of federal medical commitments, reveals administrative weaknesses and proposes drastic remedies. It is timely, because this country has reached the point where its bankruptcy in either money or manpower can cost mankind that freedom for which it is desperately fighting throughout the world.

> The United States gives varying degrees of (medical) care to 24,000,000 beneficiaries — about one-sixth of the nation. . . . . Four big and some forty smaller agencies of the government spent about one and one quarter billion dollars for health and medical services in fiscal year 1948, an increase of five times over 1940, and of 20 per cent even over 1947. In 1949, the V.A. alone will spend as much as all forty-six agencies did in 1948 — half of it for new hospitals. . . . This enormous and expanding enterprise is *devoid of any central plan.*

The Government is competing against itself. Not only are federal hospitals being built alongside existing unused federal hospitals, but also they are being built in places where they cannot be staffed. "Nearly half of the 89 new V.A. hospitals are being built or planned in areas where experience has proven that it will be difficult, if not impossible, to secure adequate staffs." Construction is far outrunning medical manpower. "In the V.A. alone, 5,600 beds are now closed because of inability to staff them." The armed-forces expansion program, on which peace is believed largely to depend, faces shipwreck on the rock of medical-manpower shortage, both quantitative and qualitative. In the race for manpower to serve a sixth of the nation the federal agencies are competing not only against one another but also against the five sixths now receiving federal aid under the recent Hill–Burton Act.

Unpalatable remedies are courageously and unanimously proposed by the Voorhees Committee. Waste must be eliminated, existing manpower must be efficiently used. Only by a unified system of federal hospitals can high-quality care in peace and national protection in war be achieved. Many federal hospitals, including Veterans Administration, Public Health Service and certain military general and even station hospitals at home, will be regrouped under a new nonmilitary Cabinet Department.

> Our area surveys, which covered about one-sixth of the country's Federal hospital beds, showed that new construction costing over $100,000,000 could probably be saved in these areas alone by such a plan. . . . Except in war, if adequate care is to be given, specialists must be utilized in their home communities.

The armed forces, merged or unmerged, will retain military hospitals overseas and certain large

medical centers and certain small installations at home posts in remote districts, but unnecessary duplication will be avoided and supervision will be exercised by a deputy of the Secretary of Defense aided by an advisory committee including civilian doctors.

There will be a unified medical supply system for all federal depots. Efforts to control and eliminate disease will be intensified. Medical research and training will cut across boundaries of service, department and government. The report ends:

> We have attempted to outline a method which we hope will correct the extravagance resulting from the present series of unrelated projects, and weld these together into an integrated, orderly whole. With such an organization, staffed with outstanding personnel, it should be possible to utilize our unequaled medical resources to the maximum, and by intelligent planning take steps which will make us a healthier and stronger nation.

If these proposals sound Utopian it means that they are being viewed from a parochial or traditional position that no longer exists in hard reality. They must be considered in the light of a world situation, critical now, and bidding fair to remain so for years. No resting place has been reached on the climb toward security and freedom. The sacrifices ahead may be greater than those behind. Apathy is to be expected. Opposition is to be expected, both sincere and cynical. Understandably, life-long traditions and habits of thought will be hard to change, and all honest doubts arising from this quarter will merit sympathy and respect. Regarding opposition motivated by conscious self-seeking, no comment need be wasted. All but two of the first forty nation-wide editorials acclaimed the Voorhees report with enthusiasm; two were critical or neutral. Admittedly, this is only a beginning, but it appears to point the right direction. Those who presently face perplexing problems of medical and financial readjustment will want to read this report and draw their own conclusions.

CATARACT IN CYCLOTRON WORKERS

The recognition of cataracts apparently related to exposure to irradiation in 5 of the pioneer physicists working with cyclotrons brings a sad reminiscence of the early workers with x-rays and radium. However, there is a point of contrast. Cataract is a condition that can usually be operated upon and corrected successfully. The skin changes and the changes in the hematopoietic tissue of the early x-ray workers could not be corrected.

At the present time studies have not progressed to the point where any common factor in these cases, other than exposure to radiation from the cyclotrons, has been determined. However, there is some evidence that exposure of the eyes to neutrons if the worker looks into the beam of the cyclotron or directly into the target area is an important factor. This practice, once possible, has been eliminated by adequate safeguards.

It has been clearly established by experiments carried on under both the Manhattan Engineering District and the Atomic Energy Commission that, on the basis of the present methods of physical measurement, the biologic effectiveness of a given dose of neutrons as measured by physical means is greater than that of roentgen rays or gamma rays by a factor of 8 or 10 at least. This greater effectiveness hinges on the nature of the neutron, which carries no external electric charge, penetrates tissue readily and may hit several atoms, producing ionization at each hit.

One of the unfortunate aspects of the development of these cataracts is that they apparently were in a sense needless — that is, some persons at least departed from the known safety standards for operation and took what might be called a calculated risk (exceeding the known permissible dose of 0.1 r per day) deliberately to expedite the scientific work on which they were engaged. One of the continuing problems of all physicians and biophysicists having to do with safety monitoring is to counteract the natural enthusiasm of the scientist, which leads him to attempt shortcuts that appear reasonable from the standpoint of his science but are unsafe from the standpoint of biologic experience. In a sense, in establishing standards of permissible dose some recognition of this has been made since the standards under which the Atomic Energy Commission and its contractors operate, for example, are set with a very appreciable factor of safety. The standards permit continuing exposure over twenty or thirty years' time, with

safety. Research is being initiated to determine the sensitivity of the lens to neutrons. It has already been established as the most sensitive structure in the eye to roentgen rays.

It is perhaps worth noting that in the making and handling of about 2½ pounds of radium up to 1941, the total amount then isolated in the world, about 100 deaths may be ascribed to radium; only 2 deaths may be ascribed to the handling of material equivalent to hundreds of tons of radium under the Manhattan Project and the Atomic Energy Commission.

THE NATURAL HISTORY OF DISEASE

MAN is subject to a great variety of diseases and it has always been one of the main functions of clinical research to provide accurate descriptions of these various pathologic entities. The characteristics of most acute diseases and of the acute phases of most chronic diseases have been reasonably well defined. With some notable exceptions, however, accurate descriptions of the entire courses of common, chronic conditions are woefully lacking.

Essential hypertension is a case in point. It is known that some patients with this disease rapidly develop incapacitating symptoms and that others go for many years without inconvenience of any sort. It is also known that some patients develop a type of hypertension that proceeds with such extreme rapidity and is associated with such extensive vascular damage that the process is quite properly designated malignant. The outlook for the patient with this form of the disease is undeniably bad, but what of the prognosis in a case of ordinary benign essential hypertension? Some investigators regard any type of hypertension as a highly dangerous disease, and believe that the prognosis is relatively poor. The practicing physician is more apt to view mild or even moderate elevations in blood pressure with less alarm, knowing that many patients with hypertension remain asymptomatic for decades. Neither view regarding the outlook in benign essential hypertension can be proved right or wrong, since most clinical descriptions of the disease cover too short a period in its course or are based on more or less selected case material. That more adequate studies are needed is very clear indeed, particularly to anyone who wishes to compare a group of treated with a group of untreated cases. The advocates of sympathectomy for the treatment of benign essential hypertension have amassed an impressive amount of data on the effects of the operation up to ten years after surgery. Unfortunately, it is still not possible to prove unequivocally that this or any other type of treatment significantly lengthens the life of the patient with benign essential hypertension. What is lacking is a long-range study of a large number of unselected and untreated cases of the disease to serve as a base line. The recent studies by Burgess[1] and by Bechgaard[2] are steps in the right direction, but many questions still remain unanswered.

Another prominent example is duodenal ulcer, the natural history of which remains shrouded in uncertainty and in which, as in essential hypertension, the value of the several forms of therapy cannot be determined until the course of the untreated disease is accurately mapped. Still another example is glomerulonephritis, although many of the more pressing questions regarding the disease have recently been answered by Addis[3] by means of a long-range study. Cardiovascular degenerative disease is at last the focal point of an integrated attack by a group of investigators whose plans call for a ten-year period of study.[4]

It is understandable, in view of the numerous difficulties involved, that relatively few investigators have undertaken long-range studies of disease. Certainly, the general methods used by Addis and by Bechgaard are to be emulated when possible, but there are other approaches to these problems. There is, for example, a vast store of information locked up in the record rooms of hospitals and outpatient departments that could and should be ferreted out. A record survey, particularly if combined with a determined attempt to follow up patients whether dead or alive, may prove to be an extremely valuable contribution. Although the results of such a study may not be entirely applicable to a community as a whole, they at least provide information covering the hospital or outpatient-department population. Record research of this type is often looked upon as the stepchild of medical

investigative endeavor, but if pursued critically it always yields information of value. Furthermore, unless such use is made of hospital records, the careful recording and filing of clinical data loses much of its value and becomes increasingly hard to justify.

Data obtained by the military services can provide a starting point for inquiry into the natural history of certain diseases in young men. Several major research projects, utilizing such data, have been initiated by the Veterans Administration. Furthermore, life-insurance statistics, although often based on highly selected samples, cannot be dismissed as valueless if the findings are not too broadly applied.

The time has surely come when the large gaps in the knowledge of long-term diseases should be closed. Not only should more long-range study projects be set up but also the data already at hand should be arranged and organized so as to obtain all possible information from it. It is decidedly paradoxical that so much investigative effort should have been spent on therapy when so little is known about the diseases against which the therapy is directed. The present trend toward long-range studies should remove the paradox and may go far toward enabling investigators to devise more rational and effective therapeutic methods.

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3. Addis, T. *Glomerular Nephritis: Diagnosis and treatment.* 338 pp. New York: Macmillan Co., 1948.
4. Keys, A. Mode of life and development of heart disease: research for preventive hygiene. *Bull. Chicago Heart Assn.* **26**:3-6, 1948.

FELLOWSHIP FOR FREEDOM

A "Fellowship for Freedom in Medicine," according to the *British Medical Journal*,* was formed by 700 British physicians at Caxton Hall, Westminster, on Saturday afternoon, November 13, 1948, Lord Horder being "unanimously acclaimed to the chair." The meeting was the eventual response to a letter from Lord Horder printed in the *British Medical Journal* in June; some 1750 letters had already been received as a result of this communication, and they were still arriving at the rate of 15 to 20 a day.

Among the reasons for the surrender of British medicine in the summer, Lord Horder averred, were "a secretariat swollen in numbers and influence; much going and coming between it and Whitehall; too strong a tail wagging too weak a dog; machinations, thought by many to be both meddlesome and mischievous, on the part of men holding key positions outside the [British Medical] Association" — (applause) — "and, if I may plagiarize Milton, 'blind mouths' at the centre and at the periphery 'hungry sheep' looking up but not being fed."

Part of the cause of the collapse, Lord Horder stated, was lack of an appreciation by the medical profession of its value in society. Its members let themselves be used "as pawns in the game instead of being master pieces."

"We are no longer experts," the chairman continued. "We sit and sign forms. With no time to diagnose their diseases, we pass our patients to other persons and to institutions, knowing full well that these cannot dispense the health benefits which may or may not be needed."

The sense of the meeting was that the standard of medical practice had fallen and was likely to fall still further; that the Fellowship for Freedom in Medicine should be in the nature of a guild to nurture the ideals of the profession until it might again be free.

British medicine may have become enslaved by politics, but it is apparently struggling inside its chains. Let American medicine look to itself that it may preserve its own freedom.

*National Health Service. Fellowship for freedom in medicine. Supplement to the *British Medical Journal* **2**:180, 1948.

EASTER SEAL CAMPAIGN

The Bay State Society for the Crippled and Handicapped, Inc., opens its fourth annual Easter Seal campaign today. The purpose of the drive is to raise $275,000 — an increase of approximately $73,000 over last year's receipts — for the support of six major treatment centers in the Commonwealth, as well as a program of medical care and employment for disabled persons, summer-camp vacations for handicapped children and prosthetic

devices for cripples. The projects operated or partially supported by this organization include a nursery school in Boston for children with cerebral palsy, a seizure unit at the Children's Hospital for the diagnosis and treatment of epilepsy, a curative workshop for the rehabilitation of the orthopedically handicapped and treatment and training centers for patients with cerebral palsy.

There is no denying the value — to the patient and the community alike — of rehabilitation and training of disabled persons. The campaign, whose success will ensure continued functioning of these vitally necessary activities, deserves the active support of physicians and laymen alike.

CORRESPONDENCE

OCCUPATIONAL MEDICAL CLINIC AT MASSACHUSETTS GENERAL HOSPITAL

To the Editor: From 1911 to 1928 the Massachusetts General Hospital conducted what was known as the Industrial Clinic for the study and care of workers thought to be disabled because of occupational hazard.

On February 1, 1949, this work was revived at the Massachusetts General Hospital with the slightly broader title, Occupational Medical Clinic. Supported by funds from the National Institute of Health, Research Grants Division of the United States Public Health Service, and the Massachusetts General Hospital, the work is to be investigative in nature. Affiliation of the Occupational Medical Clinic with the Massachusetts Division of Occupational Hygiene will make possible correct evaluation of the hazards in the worker's environment capable of causing disease. Inpatient study in a small way is planned, and outpatients will be seen regularly at the request of any physician. No traumatic cases will be handled. Proper diagnosis, delineation of previously unrecognized occupational illness and study of better forms of management of worker disability are the concern of the Occupational Medical Clinic. After study, worker patients will be referred to their private physicians for care. The initial visit will be on a regular outpatient basis, but no charge will be made to patients who are accepted for study in the Occupational Medical Clinic, since this is a research project.

N. W. Faxon, M.D., *Director*
Massachusetts General Hospital
Boston

NOTICES

TOWN MEETING OF DOCTORS

A Town Meeting of Doctors will be held at the Massachusetts General Hospital, Lower Out-patient Department Amphitheater, on Monday, March 21, at 8 p.m. There will be a discussion of controversial issues from Mr. Ewing's report "The Nation's Health — A Ten-Year Program." 2. Enough Hospitals Everywhere.

COUNCIL OF THE NEW ENGLAND STATE MEDICAL SOCIETIES

A meeting of the Council of the New England State Medical Societies will be held in the Oval Room of the Copley Plaza Hotel, Boston, on Sunday, March 27.

Program

1:30 p.m. Call to Order.
Greetings. Stephen A. Cobb, M.D., president, Council of the New England State Medical Societies and past president, Maine Medical Association.
1:45 p.m. The National Education Campaign of the American Medical Association. Clem Whitaker, campaign director, and Leone Baxter, general manager.
2:45 p.m. The Special A. M. A. Assessment. James R. Miller, M.D., Trustee, American Medical Association, and past president, Council of the New England State Medical Societies.
3:15 p.m. Extending Medical Care in New England through Medical-Society Sponsored Voluntary Plans. (A five-minute report by a delegate from each of the six state medical societies.)
3:45 p.m. Extending Medical Care in New England through Insurance-Company Programs. Henry D. Locke, research director, Liberty Mutual Insurance Company, Boston.
4:15 p.m. Discussion from the Floor. (Officers and Committee members of state and county medical societies are invited to discuss the topics presented, and to ask questions of the speakers.)
5:15 p.m. Adjournment.

NEW ENGLAND HEART ASSOCIATION

A meeting of the New England Heart Association will be held in the Auditorium of Building E, Harvard Medical School, on Monday, March 28, at 8:00 p.m., Doctor Herrman L. Blumgart presiding.

Program

Experimental Fluorocardiography with Simultaneous Recording of Intracardiac Pressure. Drs. Aldo A. Luisada and Felix G. Fleischner.

Appraisal of the Size of the Right Ventricle in the Lateral View. Dr. Felix G. Fleischner.

Spontaneous Cardiac Rupture: A clinicopathological study of fourteen cases. Drs. Stanford Wessler, Monroe J. Schlesinger and Paul M. Zoll.

Experimental Studies of the Cardiac Action of Quinidine. Dr. Arthur J. Linenthal.

The Role of Anemia in the Production of Interarterial Coronary Anastomoses. Drs. Paul M. Zoll, Monroe J. Schlesinger and Stanford Wessler.

Treatment of Euthyroid Cardiac Patients by Producing Hypothyroidism with Radioactive Iodine.

The Method of Producing Hypothyroidism. Drs. A. Stone Freedberg, George Kurland and Alvin L. Ureles.

Clinical Results in Angina Pectoris and Congestive Failure. Drs. Herrman L. Blumgart, A. Stone Freedberg and George Kurland.

To complete the program by 10:00 p.m., the meeting will begin at 8:00 p.m.

Interested physicians and medical students are cordially invited to attend.

ALUMNI OF CHILDREN'S HOSPITAL, WASHINGTON, D. C.

An organization of the Alumni of Children's Hospital, Washington, D. C., is being undertaken. The Children's Hospital Alumni Charter Meeting will be held on April 5 in Washington, D. C.

Further information may be obtained from Dr. Alfred T. DeVito, chairman of the Organization Committee, Alumni Association, Children's Hospital, Washington, D. C.

THE FOUNDATION PRIZE

An award entitled "The Foundation Prize" has been established by the South Atlantic Association of Obstetricians and Gynecologists. Authors of papers on obstetric or gynecologic subjects desiring to compete for the prize may obtain information from Dr. E. D. Colvin, secretary-treasurer, South Atlantic Association of Obstetricians and Gynecologists, 1259 Clifton Road, N. E., Atlanta, Georgia.

(*Notices concluded on page xiii*)